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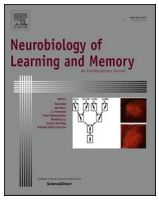

Engrams across diseases: Different pathologies – unifying mechanisms?☆

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ABSTRACT

Memories are our reservoir of knowledge and thus, are crucial for guiding decisions and defining our self. The physical correlate of a memory in the brain is termed an engram and since decades helps researchers to elucidate the intricate nature of our imprinted experiences and knowledge. Given the importance that memories have for our lives, their impairment can present a tremendous burden. In this review we aim to discuss engram malfunctioning across diseases, covering dementia-associated pathologies, epilepsy, chronic pain and psychiatric disorders. Current neuroscientific tools allow to witness the emergence and fate of engram cells and enable their manipulation. We further suggest that specific mechanisms of mnemonic malfunction can be derived from engram cell readouts. While depicting the way diseases act on the mnemonic component – specifically, on the cellular engram – we emphasize a differentiation between forms of amnesia and hypermnesia. Finally, we highlight commonalities and distinctions of engram impairments on the cellular level across diseases independent of their pathogenic origins and discuss prospective therapeutic measures.

1. Introduction

Memories are the cognitive foundation of our existence. They are our reservoir of experiences, helping us to shape our personality and defining who we are as individuals. Hence, there is a strong emotional component attached when talking about memories from a non-scientific point of view. For example, remembering certain epochs of our life brings back almost the same joyful or painful emotions that we experienced before. Taking a view from a rational perspective, memories ensure our survival. They evoke past experiences of food sources or threats, helping animals, including humans, to navigate through environments and make informed decisions. As memories are fundamental throughout lifetime in every species, their loss or alteration presents a tremendous burden. Diverse diseases of the central nervous system are accompanied by the malfunction of memories as major or minor symptoms. To understand how memories are acquired, consolidated, retrieved, updated and forgotten, scientists make use of the concept of an engram.

The term engram is used to describe the physical trace that a memory leaves in the brain after learning, to be later retrievable as required. The idea that experiences must be imprinted in the brain in order to become retrievable as memories was already raised by the ancient Greeks, and elaborately postulated first by Richard Semon in 1904 (Semon, 1904). Today, this idea is a validated concept. Excellent gain- and loss-of-function studies revealed that it takes no more than activating (Liu et al., 2012) or inhibiting (Tanaka et al., 2014) engram cells optogenetically to e.g. retrieve or supress a specific memory in hippocampal dentate gyrus (DG) and cornu ammonis 1 (CA1), respectively. However, even today as the development of neuroscientific tools has grown exponentially, we are still a long way from understanding the full complexity of memories and their manifestation in the brain. In our current view (and for the scope of this review) engram cells are a population of neurons that becomes activated and to a certain extent reactivated during a learning event and when the memory is retrieved, respectively. The activity upon learning is accompanied by plasticity processes that shape the involved circuits. Activating or silencing this

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population of neurons can recall or suppress the memory-associated behavior. With our definition we are in agreement with the description of (Josselyn & Tonegawa, 2020), who further state: "Engram cells (…) constitute critical cellular components of a given engram. These cells may (or may not) also be critical components of engrams supporting other memories".

When we previously investigated the fate of the engram in a mouse model of Alzheimer's disease, mimicking the amyloid pathology, we found the mechanism of memory impairment to be engram interference (Fig. 2, see also section 4.1). We speculated that this might be a general mechanism for forgetting. Moreover, we detected some interesting mechanistic parallels to diseases with a different pathogenesis, like Rett syndrome (section 4.2). This made us curious to look more thoroughly at the literature focusing on engram malfunctioning on the cellular level across diseases and summarizing our knowledge journey in this review article. For this purpose, we will briefly summarize the current framework of engram knowledge and mention available tools to study engrams. We will then discuss engram cells in dementia-associated diseases (section 4), epilepsy (section 5), chronic pain (section 6) and psychiatric diseases (section 7), and embrace the variability that engram malfunctioning can underly. Finally, we highlight commonalities and distinctions between mechanisms of engram malfunctioning, associated with forgetting or involuntary recall (section 8) and discuss prospective therapeutic measures in humans (section 9). The scope of this review is not to describe every disease in its full complexity, but rather focus specifically on mechanisms of engram cell impairment and thus, dive into detail where applicable and necessary for the purpose of completing the picture or bridging diseases. For some diseases mentioned by us, cognitive impairment is not the major symptom, yet relevant enough to elucidate mechanisms of engram impairments. As available neuroscientific tools are bound to pre-clinical research, the majority of studies mentioned were conducted in rodents. However, we dedicated a paragraph discussing potential translational approaches to our species at the end of this article. Studying memory in the light of engrams is beneficial to better understand how diseases impair learning and memory processes, and potentially pave the way to discuss the development of precise treatments for disease-associated memory malfunctioning.

2. Engrams – A curse and a blessing?

An engram is a concept to grasp the intricate nature of memories. Finding physical correlates may help to elucidate the phenomenon of memories and their various aspects, in health and disease. On the other hand, the use of concepts for the purpose of simplification can also restrict the scientists' view on the underlying complex truth. Originally, engram studies visualized cellular immediate early gene (IEG) expression (see section 3) as proxy for a functionally relevant neuronal population. With emerging neuroscientific methods, it became possible to further interrogate and manipulate IEG expressing neurons e.g. by the help of opto- and chemogenetic tools. Moreover, closed-loop experimental approaches that enable real-time targeting of neuronal populations allow to probe their relevance for memory expression on the behavioral level (Schweihoff et al., 2021). Yet, there is more complexity in the term engram, than being composed of an IEG-expressing cellular entity (Fig. 1). According to the memory allocation theory, whether a neuron will be allocated to an engram or not, is determined by the cell's predisposition, e.g. inherent excitability (Mocle et al., 2024; Yiu et al., 2014), CREB (cAMP response element binding) protein expression (Josselyn & Frankland, 2018; Zhou et al., 2009) and chromatin plasticity (Santoni et al., 2024). Allocation mechanisms are hypothesized to go hand-in-hand with the following plasticity processes (Lisman et al., 2018). Upon learning further gene expression (Kandel et al., 2014), functional and structural synaptic plasticity (Citri & Malenka, 2008), but

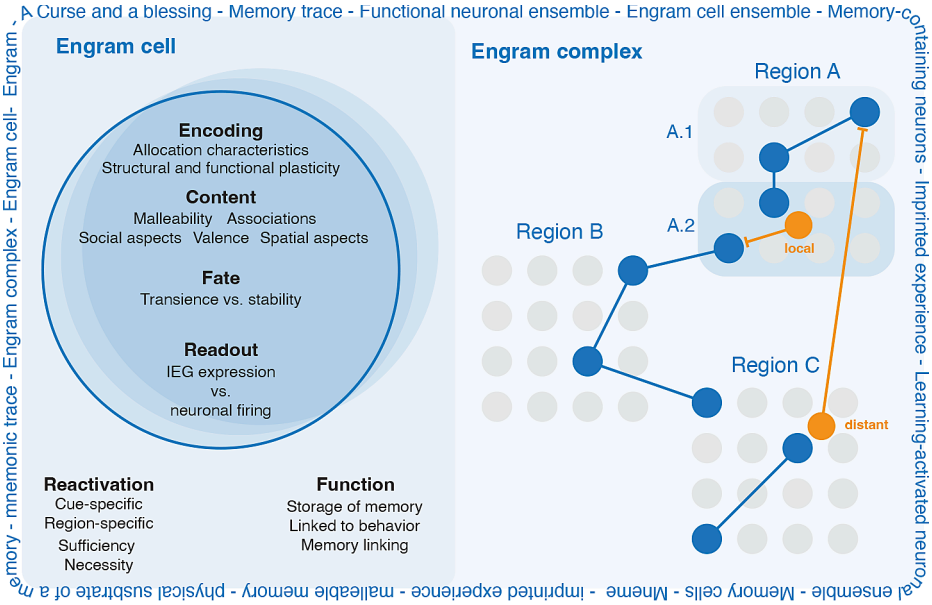

Fig. 1. A curse or a blessing — the multifaceted aspects of an engram. When Richard Semon brought up the term "engram" it was a theoretical concept about how memories might be imprinted in our brain. Decades later, engram cells and their potential contribution to engram complexes are characterized in a way to allow their connection to and interpretation in the context of behavior. Different stages of the engram cell life cycle can be distinguished: during encoding various allocation mechanisms determine which cells are recruited as engram cells and thus, undergo plastic changes on the molecular and structural level. During its lifetime the content of an engram and its associated valences can change and ultimately be lost, due to natural or pathological forgetting. Readouts to study engram cells mainly comprise the visualization of immediate early genes (IEGs), but also comprise recording neuronal firing. Engram cells are known to be partly reactivated if the memory is recalled. This reactivation process is cue- and region-specific and moreover meets the attributes of sufficiency and necessity for a given memory to be expressed. Engram cells are thought to not exist as single entities, but rather occur within engram complexes, i.e. engram cells across brain- (e.g. Regions A to C) and associated subregions (here: A.1 and A.2). Moreover, inhibitory interneurons can function as engram cell and/or further mediate engram formation and recall, either by acting locally, or from distal regions through long-range projections. The various wording used to describe the physical correlates of memories stresses the urge for a standardized assignment.

(caption on next page)

Fig. 2. Mechanisms of engram malfunctions. Six mechanistic malfunctions on the engram cell level can be compiled across diseases, covering dementia-associated pathologies, epilepsy, chronic pain and psychiatric disorders. The presented mechanisms can be further grouped into mechanisms causing the loss (amnesia) or prolonged maintenance (hypermnesia) of memories. Putative engram cells and associated malfunctions are visualized at two stages, during learning and recall. We expect the initial engram during learning to be partly reactivated during recall (physiological). However, the exact extent of reactivation depends on the particular brain region and is not reflected here. Neuronal loss lies at the extreme end of a complex spectrum of memory impairments and mostly occurs in advanced disease stages. The loss of neurons is severe and well characterized e.g. in AD and PD. However, the causal connection to the loss of engram cells and resulting memory impairments has not been shown. Interference is described by the activation of an additional neuronal population during recall, apart from the engram, rendering the engram cells "inaccessible" and ultimately resulting in an unsuccessful memory recall. Reactivation impairment refers to a deficiency in engram reactivation during recall. The source of this defect can be due to impaired learning-associated plasticity during encoding, faulty consolidation or reconsolidation. An impairment of engram cell recruitment is the earliest point in time an engram can be affected and ultimately results in memory impairment. Over-encoding is associated with excessive recruitment of engram cells during learning and thus leads to a higher engram cell density during recall. Pathological association occurs when a negative experience (e.g. chronic pain or seizure) is allocated to a distinct memory engram. Upon reactivation of the engram, the memory of the negative experience or the experience itself is recalled. In the context of epilepsy, pathological association is hypothesized to be involved in the ictogenesis, i.e. the initiation of seizures. AD, Alzheimer's disease; PD, Parkinson's disease; MDD, major depressive disorder; FXS, Fragile-X-syndrome; PTSD, post-traumatic stress disorder. We marked diseases with an asterisk for which existing data are suggesting a mechanism of engram malfunction, but engram-specific experimental evidence is missing.

also, epigenetic changes (Coda & Gräff, 2024) and double-stranded DNA breaks and repairs (Jovasevic et al., 2024) take place. These processes happen within cellular ensembles, as well as downstream, to further shape engram-associated neuronal circuits. Also, inhibitory neurons can be a part of the engram itself (Barron et al., 2017), acting locally or via long-range inhibitory projections (Fig. 1). Their connectivity is known to be shaped by excitatory neuronal activity, potentially adapting neuronal circuits to external demands (Yap et al., 2021). It was further shown that glial cells modulate memory by interacting with engram cells. Astrocytes were e.g. shown to differently affect the strength of recent and remote memory recall (Refaeli et al., 2024). Microglia, the resident immune cells of the brain, are critically involved in modulating the duration of memories by complement-dependent synaptic elimination (Wang et al., 2020), probably due to their ability to show neuronal activity-dependent behavior (Nebeling et al., 2023). According to the modern understanding of Semon's engram concept, the storage site of a given memory is not a single engram cell population in a particular brain region, but a "unified engram complex" consisting of connected networks of engram cell ensembles, distributed across different brain regions (Josselyn & Tonegawa, 2020; Roy et al., 2022; Tonegawa et al., 2015) (Fig. 1). Over time, engrams might be transformed by plasticity-related changes (Bailey et al., 2015) or neurogenesis (Ko & Frankland, 2021).

We further believe that discussing engrams across scales is crucial to gain a deeper insight into the mechanisms of engram formation and fate, also in the context of memory malfunction. Therefore, we included studies with varying readouts and aimed at bridging the gap of scales by finding points of intersection in the context of the diseases discussed here. An in-depth discussion of this topic has been given elsewhere (Yuste et al., 2024). It is moreover crucial to regard the engram as brain region-specific phenomenon. As we appreciate the complexity of every brain region that is given by its cell-type composition, functional role and intra- and interconnectivity, we have to take this into consideration when talking about engrams. There are numerous examples of region-dependent engram characteristics, e.g. engram sizes, rate of reactivation upon recall or correlation of reactivation and memory performance. To give some examples, upon fear conditioning roughly 15 %, 5 % or 2 % of neurons are expressing c-Fos in CA1, DG or the BLA, respectively (Tayler et al., 2013). The extent of engram cell reactivation (overlap of IEG expressing cells of two events) in the BLA is dependent on associative learning (Reijmers et al., 2007), whereas in hippocampal CA1 also non-associative learning causes reactivation (Guzowski et al., 1999). Engram reactivation in BLA, but not LA, correlates with freezing upon conditioned context exposure (Reijmers et al., 2007). Notably, terminology varies and is often used inconsistently depending on the specific method used to study the physical correlates of memory. Consequently, different hypothesized functions are assigned to these terms. "Engram cells" are read out mostly by IEG expression and are suggested to encode memories, whereas "neuronal ensembles" are read out by neuronal firing (e.g. approximated by recording Ca^{2+} influx) and are suggested to encode e.g. perceptual states and awareness (Yuste et al., 2024), without being mutually exclusive. Neuronal ensembles can function as engrams and vice versa. Whether or not the investigation of engram cells is a useful proxy to understand the brain and treat diseases that involve mnemonic dysfunction is an ongoing debate. Similar to other researchers (Denny et al., 2017; Ryan & Frankland, 2022), we believe that the concept of an engram is indeed helpful and reasonable to be used studying memories and their fate across diseases. Whether this will yield translatable tools to account for mnemonic malfunction in humans, is yet to be determined. Across diseases, we identified six mechanisms of engram cell malfunctioning: neuronal loss, interference, reactivation impairment, recruitment impairment, over encoding and pathological association. Engram cells are commonly investigated after two discrete events, i.e. learning and recall. We therefore decided to visualize mechanisms of engram cell malfunction based on these two events (Fig. 2). We will now briefly cover engram tagging strategies, before we dive into diverse diseases, selected by their characteristic to act on mnemonic processes and by the availability of engram-centric literature.

3. Engram tagging strategies

The activity-dependent, permanent expression of a fluorophore or neuroscientific tool is often referred to as "tagging". The purpose of tagging is either, to visualize and/or manipulate engram cells to investigate their role in mnemonic processes. To capture engrams scientists widely make use of immediate early genes (IEGs). IEGs are transcribed in response to neuronal activity and therefore serve as a proxy of recently activated cells (Sagar et al., 1988; Yap & Greenberg, 2018). However, IEGs are not just markers of recently active neurons (and glia), but also and primarily function as biological entities, e.g. as transcription factors, postsynaptic proteins or secretory factors (Okuno, 2011). The most broadly studied and used IEG is *c-fos*, a member of the Fos family of transcription factors. Besides *c-fos*, *Arc*, *Egr1* and others allow the capture of engrams (Korb & Finkbeiner, 2011; Saha et al., 2011). The discovery of IEGs opened the door to a variety of interesting tools: identification of recently active cells by visualization of expressed IEGs via immunohistochemistry or their transcripts via RNA fluorescent *in situ* hybridization (RNA-FISH). Moreover, by using the varying temporal expression profiles of IEG transcripts it was possible to identify the overlap of neuronal populations engaged during two discrete events close in time (catFISH, cellular compartment analysis of temporal activity by fluorescent in situ hybridization) (Guzowski & Worley, 2001). *In vivo*, the expression of fluorescent proteins under the IEG promotor (Barth et al., 2004; Eguchi & Yamaguchi, 2009) visualizes engram cells and longitudinal imaging over days or weeks (e.g. by two-photon microscopy) helps to understand the dynamics of engram circuits (Poll et al. 2020). IEG-dependent expression of chemo- or optogenetically activatable receptors allows for the manipulation of functionally related cells (Emiliani et al., 2022; Roth, 2016). To increase the expression level

of the gene of interest synthetic promoters were developed that comprise activity-responsive enhancer elements and IEG minimal promoters. For example, E-SARE (enhanced synaptic activity-responsive element), which is based on *Arc's* strongest enhancer and was shown to drive neuronal activity-dependent gene expression more potently than other IEG promoters (Kawashima et al., 2013; Kawashima et al., 2009).

Crucial for event-specificity of the tagging procedure is a restricted time window, which can be achieved by a drug-dependent control of the expression window. Namely, two approaches are commonly used: (1) the TetTag system and (2) the TRAP system. The TetTag System comprises an IEG-dependent expression of the tetracycline-controlled transactivator (tTA) that subsequently drives expression of a construct of interest by binding to the tetracycline responsive element (TRE) (Shockett & Schatz, 1996). The tagging window is temporally controlled by the presence (Tet on) (Gossen et al., 1995) or absence (Tet off) (Mayford et al., 1996) of doxycycline (Reijmers et al., 2007). The TetTag system can be delivered e.g. by a combination of a transgenic mouse and AAV delivery (Liu et al., 2012) or via two AAVs (Poll et al., 2020). An improved system that relies on the same principle is the Robust Activity Marking (RAM) system (Sørensen et al., 2016). Especially through an optimized *c-fos* promoter and a modified Tet off system, RAM allows for a higher sensitivity and selectivity. Moreover, it is compact enough to be packed into one AAV. The TRAP system is available as a transgenic mouse line that expresses a tamoxifen-inducible Cre recombinase under the *c-fos* promoter (DeNardo et al., 2019; Guenthner et al., 2013). The tagging window is determined by the actions of tamoxifen or OHT (Cazzulino et al., 2016) that led the Cre recombinase to enter the nucleus and elicit its action.

While these systems with drug-inducible expression windows have a limited temporal resolution (hours to days), new expression systems have been developed that depend on the coincidence of two very fast events, i.e. calcium influx into the cell and light delivery (seconds to minutes). CaMPARI (Calcium-Modulated PhotoActivatable Ratiometric Integrator) is a fluorescent protein that irreversibly changes its emission wavelength from green to red in the presence of high intracellular calcium concentrations and simultaneous exposure to blue light. The photoconversion makes it possible to take a "snapshot" of active neurons at a specific timepoint (Fosque et al., 2015). However, to allow for the expression of a tool of interest, further systems have been developed: e.g. Cal-light (Lee et al., 2017; Sanchez & Ting, 2020), FLARE (Fast Light- and Activity-Regulated Expression) (Wang et al., 2017), single-chain FLARE (scFLARE) (Sanchez et al., 2020) and FLiCRE (Fast Light and Calcium-Regulated Expression) (Kim et al., 2020). All four systems are based on the same principle: if both events, a high intracellular calcium concentration and the presence of blue light, coincide, a transcription factor is released, which subsequently drive the expression of a gene of interest, e.g. a fluorophore or a neuroscientific tool.

Tagging of engram cells might lead to an over- or underestimation of the neurons participating in an engram, as available tagging systems often suffer from background expression and/or do not reach the entire engram cell population (Li & Yang, 2023). While the temporal resolution for the tagged neuronal population is improved with Cal-light, FLARE, scFLARE and FLiCRE, these approaches require the delivery of light to the region of interest and thus, an often more invasive experimental procedure. Overall, the major limitations of engram tagging tools affect their temporal resolution, specificity and sensitivity. Systems are constantly developed further, see also (Pang et al., 2023) for a recent review article covering engram tagging strategies. Despite the tremendous contribution of tagging tools to our current engram knowledge, it is advisable to probe their function and eligibility for each specific application.

Given that most engram tagging studies mentioned in this review article are based on IEG-dependent tagging strategies, it is of note that autonomous activity of a neuron alone is not necessarily sufficient to drive gene expression (Anisimova et al., 2023). The evocation of gene expression is yet a sign for a strong and relevant event and thus, to be interpreted differently to a neuronal spike or a calcium influx event, as a proxy for neuronal firing. Some studies aimed at closing the gap between the scales of activity (e.g. approximated by calcium influx) and IEG expression (e.g. c-Fos) (Pettit et al., 2022; Tanaka et al., 2018). It was shown that experience might alter the relationship of both, also depending on the brain regions and their functional roles. For example, monitoring place cell activity (i.e. cells that fire at a specific location in a given environment) and IEG expression in the same population of CA1 neurons, revealed different relationships of both depending on whether the mice explored a familiar or novel environment (Pettit et al., 2022; Tanaka et al., 2018). While keeping in mind that IEGs are an indirect marker for summed neuronal activity, they unequivocally made groundbreaking discoveries possible and revolutionized the engram field.

4. The engram in dementias – Mechanisms of impairment beyond cell loss

4.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia affecting more than 55 million people world-wide (WHO, 2021). It manifests as an early impairment of memory and cognition. While initially short-term memory is affected, long-term memory becomes impaired additionally in the later stages. Neuropathologically, AD is characterized by the deposition of extracellular senile plaques (Glenner & Wong, 1984) and intracellular neurofibrillary tangles (Grundke-Iqbal et al., 1986). Senile plaques are composed of amyloid beta that aggregated due to alternatively processed amyloid precursor protein. Neurofibrillary tangles are aggregated microtubuli, that lost their integrity due to hyperphosphorylated tau. It is hypothesized that both deposits act together to affect the balance of excitation and inhibition, finally causing a general network dysfunction (Palop et al., 2006) and eventually cell loss. Moreover, an early neurite impairment (Stokin et al., 2005) and later loss of cholinergic forebrain neurons is described (Davies & Maloney, 1976) and is suggested to play an indirect, but significant role in disease-associated cognitive deficits.

For the purpose of preclinical research, animal models have been developed that mimic the genetic predisposition of familiar AD (Zhu et al., 2015). Of note, in early stages of the disease, where profound neuronal loss is still absent, a detrimental impairment of mnemonic function can already be seen. This raises the question for alternative hypotheses of factors causing cognitive deficits besides the sheer loss of neurons. For example, early synaptic changes that happen before neurodegeneration or are co-occurring with modest loss of neurons have been shown in models that mimic the amyloid-pathology in AD (Jackson et al., 2016; Jankowsky et al., 2004; Jankowsky et al., 2001). On the level of engram cells, impaired recall was associated with a reduced number of c-Fos expressing cells in DG in comparison to mice without AD-like pathology (Roy et al., 2016) (Table 1). Another study examined the number of Arc expressing cells upon recall and found no difference in comparison to healthy controls (Perusini et al., 2017) (Table 1). However, Perusini et al. revealed that the overlap of neurons active during memory acquisition and recall was reduced in mice with impaired memory. These studies support the view of an *impaired reactivation* of engram cells as source of mnemonic impairment (Fig. 2).

However, mnemonic impairments can also manifest through other cellular mechanisms. The DG is a site of adult neurogenesis in the brain, a process known to be impaired in healthy individuals during aging (Frankland et al., 2013) and AD patients (Moreno-Jiménez et al., 2019). Mishra et al. showed that memory impairment in a mouse model of AD was associated with a reduced recruitment of immature neurons into the DG engram, paired by a deficient reactivation of engram cells. Restoring neurogenesis was sufficient to rescue the memory impairment in this mouse model of AD (Mishra et al., 2022) (Table 1). Hence, this study demonstrates *impaired recruitment* as a mechanism of engram and thus

Table 1

Engrams across diseases. This table lists studies that investigate cognitive alterations on the level of engram cells, acquired in rodents. Studies are sorted by diseases with their specific pathology and examined brains region(s). Moreover, it lists the methods used to visualize and/or use cellular "activity" (in parentheses, as it is approximated by IEG expression or calcium imaging) to express tools. A mechanism of engram malfunction is hypothesized for every study, based on the reported data. Additionally, study-specific details are given that explain the assignment of the respective mechanism. Further, the strategies to manipulate the engram, either directly or indirectly, are mentioned together with the respective effect of the manipulation. We do not claim that this table is complete for every disease, but it presents a representative synopsis of explicit engram studies. AD, Alzheimer's disease; Amy, Amygdala; BLA, Basolateral Amygdala; CA1, cornu ammonis 1; CA3, cornu ammonis 3; catFISH, cellular compartment analysis of temporal activity by fluorescent in situ hybridization; CSDS, chronic social defeat stress; DG, dentate gyrus; DGCs, dentate granule cells; EE, enriched environment; HFS, high frequency stimulation; IHC, immunohistochemical analysis; LTP, long-term potentiation; MDD, major depressive disorder; NAc, nucleus accumbens; PD; Parkinson's disease; PTSD, post-traumatic stress disorder; SOM Ins, somatostatin-expressing interneurons; TRAP, targeted recombination in active populations.

Disease	Pathology	Brain region	Method	Mechanism	Mechanistic detail	Manipulation (of engram)	Effect of manipulation	Reference
Alzheimer's disease	Amyloidosis	DG	c-Fos IHC	Impaired reactivation*	Based on c-Fos IHC	Optogenetic activation	Rescue of memory deficit	Roy et al. 2016
	Amyloidosis	DG	ArcCreERT2	Impaired reactivation	Overlap of tagged and Arc-positive cells by IHC	Optogenetic activation	Rescue of memory deficit	Perusini et al. 2017
	Amyloidosis	DG	TetTag AAV, c-Fos and Egr1 IHC	Impaired recruitment	Reduced recruitment of new born DGCs	Enhancing neurogenesis	Rescue of memory deficit	Mishra et al. 2022
	Amyloidosis	CA1 (dorsal)	FosGFP mouse	Interference	Competing engram	Chemogenetic (in) activation of a competing engram	Rescue of memory deficit	Poll et al. 2020
Rett Syndrome	MECP2 KO	CA1 (dorsal)	Ca^{2+} imaging	Interference	Increased ensemble size	Chemogenetic activation of SOM INs	Rescue of memory deficit	He et al. 2022
Fragile X syndrome	FMR1 protein loss	CA1	AAV-Fos-TRAP, c-Fos IHC	Impaired reactivation	Reconsolidation deficit	Exposure to enriched environment	Rescue of memory deficit & reactivation	Li et al. 2020
Epilepsy	Seizure	DG	c-Fos IHC, EEG	Pathological association	Engram-mediated seizure	Chemogenetic (in) activation	Termination or Induction of seizures	Lai et al. 2024
	Seizure	CA1	TRAP mouse, c-Fos IHC	Recruitment impairment	Seizure induced LTP saturation impairing potential engram cell recruitment	High frequency stimulation (HFS) to induce LTP	HFS failed to potentiate the seizure-tagged neurons	Naik et al. 2021
Chronic pain	Nerve injury	BLA	TRAP mouse, Ca^{2+} imaging	Over encoding*	Hyperactivity	Chemogenetic inhibition of nociceptive ensemble in BLA	Decreased affective motivational behavior	Corder et al. 2019
	Nerve injury, Inflammation, stress (fear)	PFC	TRAP mouse, c-Fos IHC	Pathological association*	Engram cells representing nociception and tactile sensation	Optogenetic (in) activation	Reduction of pain behavior and reinforcement, respectively	Stegemann et al. 2023
MDD	Stress (CSDS)	CA1 (dorsal, ventral)	TetTag-LacZ mouse	Over encoding	Enhanced (negative) engram size	Chemogenetic (in) activation	Prevention or induction of social avoidance	Zhang et al. 2019
	Stress (fear)	CA1 (ventral)	TetTag AAVs, TRAP2 mouse	Pathological association	Chronic negative thinking	Chemogenetic activation of negative engram	Induction of anxiety-related behavior	Jellinger et al. 2024
	Stress (fear)	DG	TetTag AAVs	Pathological association	Overwriting of negative engram	Optogenetic activation of a positive engram	Amelioration of depression-like behavior (anxiolytic)	Ramirez et al. 2015
PTSD	Stress (fear)	Amy	c-Fos IHC	Over encoding	Increased allocation	Growth hormone overexpresssion by HSV	Increased number of allocated neurons	Gisabella et al. 2016
	Stress (fear)	DG, BLA	c-Fos-TtA mouse + TRE-AAV	Pathological association	Engram-associated malleable valence	Optogenetic activation of a negative engram in a positive context	Switch of engram valence	Redondo et al. 2014
	Stress (fear)	DG, CA3	c-Fos IHC + catFISH	Pathological association	/	Chemogenetic (in) activation of reccall induced engram during extinction	Impairing and facilitating extinction, respectively	Khalaf et al. 2018
	Stress (fear)	DG	TetTag AAVs	/	/	Optogenetic activation of a positive engram during fear recall	Reduction of fear	Grella et al. 2022
Addiction	Drug intake	NAc	Fos-LacZ mouse, c-Fos IHC	Pathological association	/	Daunorubicin-mediated ablation	Reduction of drug-associated locomotion	Koya et al. 2009
	Drug intake	NAc, CA1 (ventral)	Fos-tTA mouse, c-Fos IHC	Pathological association	Induction of drug-associated behavior	Chemogenetic (in) activation	Induction or reduction of drug-associated behavior	Zhou et al. 2019

memory impairment (Fig. 2).

Strikingly, the optogenetic reactivation of engram cells in DG or CA1, respectively, was sufficient for overcoming the recall deficit seen in AD-like mice (Roy et al., 2016; Poll et al., 2020). The fact that memory retrieval is possible through artificial reactivation of engram cells, but not through natural cues suggests that the structural connectivity of participating engram neurons is intact and meaningful, however, too weak to be retrieved by natural cues (Roy et al., 2016) (Table 1). Interestingly, *in vivo* two-photon imaging of a fosGFP fusion protein showed that the engram in CA1 is indeed reactivated by natural cues, despite impaired recall on the behavioral level (Poll et al. 2020). Naturally evoked reactivation of the putative engram cells, however, was not sufficient to behaviorally express the memory. An additional ensemble of cells in the recall network was interfering with the engram ensemble and thereby, impairing recall (Poll et al., 2020) (Table 1). The relative amount and characteristics of fosGFP expression in AD mice during recall resembled those of healthy mice placed in a novel context, specifically, showing an increased number of fosGFP-expressing cells with no prior activity history within the given timeframe. Thus, the dynamic observation of c-Fos expression in CA1 suggests that AD-like mice perceive the conditioned context as novel. But why does this additional activity emerge? It is unlikely that this additional ensemble activity arises by the direct presence of soluble amyloid-beta or amyloid-beta plaque-associated hyperactivity (Busche et al., 2012). We showed that the density of fosGFP expressing cells close to plaques in CA1 is similar between diseased and healthy mice (Poll et al., 2020). CA1 is thought to act as an evaluator of contextual information, comparing the current with past experiences. When healthy mice explore a novel context, CA1 pyramidal neurons were shown to be highly active on the level of spiking and c-Fos expression, broadcasting the recognition of novel environments (Larkin et al., 2014; Priestley et al., 2022; Radulovic et al., 1998) and, thus enabling an efficient encoding of these environments and their spatial aspects (Priestley et al., 2022). We hypothesized that in AD-like mice, the familiar context is wrongly evaluated as novel and thus, causing elevated fosGFP expression. These data suggest engram *interference* in CA1 as mechanistic explanation for rendering the engram inaccessible and thus, causing mnemonic dysfunction (Fig. 2).

A possible explanation for interference to impair memory includes a decreased signal-to-noise ratio in the recall network that might hinder successful information flow. Decreasing the signal-to-noise ratio in healthy animals by chemogenetic activation of a competing engram impaired recall (Garner et al., 2012). A mechanistic explanation for interference to occur includes impairments on the level of activity-dependent plasticity processes during learning and/or consolidation. These can have their origin in different parts of the neuronal circuit mediating engram formation. First, on the level of engram cell activity itself: for example, optogenetic silencing of CA1 during learning and thereby hindering plasticity, prevents memory recall (Tanaka et al., 2014) and induces an alternative engram that might take over the task to encode spatial aspects of the silenced ensemble (Trouche et al., 2016) – a mechanism to compensate for an engram impairment? Second, on the level of circuit-shaping interneurons. Under physiological conditions the number of active neurons is tightly controlled. In context of AD interneuron dysfunction has been hypothesized to be a key mediator of network dysfunction (Palop & Mucke, 2016). Key players are local inhibitory interneurons (INs), like parvalbumin (PV)-expressing basket cells, somatostatin (SST)-expressing oriens-lacunosum moleculare (O-LM) interneurons and vasoactive intestinal peptide (VIP) expressing INs (Ali et al., 2023). Dysfunction of INs may favor the raise of additionally active pyramidal cells, which has also been shown to be causal for cognitive impairment in another dementing condition with a different etiology, namely the Rett syndrome (section 4.2). One potential mechanism involves SST-expressing INs, which were shown to have reduced learning-dependent structural plasticity under AD-like conditions (Schmid et al., 2016). This phenomenon is associated with reduced cholinergic input from the medial septum. Treating mice with cevimelin, an agonist for muscarinic receptors, ameliorated the plasticity deficit and thus, learning (Schmid et al., 2016). Whether and how this rescue reveals itself on the level of engram cells is yet to be shown. Another potential mechanism involves a subtype of VIP-expressing INs that specifically target other INs. These have been shown to signal the experience of a novel context and disinhibit pyramidal cell activity to facilitate learning to take place (Tamboli et al., 2024). Interestingly, the output of VIP INs is impaired in a mouse model of AD (Michaud et al., 2024). This is a noteworthy connection to the interfering activity described above, suggesting a potential mechanism of engram impairment in AD. Third, it has been shown that c-Fos itself is rendering downstream plasticity processes that lead to an increased peri-somatic inhibition of PV-INs on CA1 pyramidal neurons (Yap et al., 2021). It is tempting to speculate that this process underlies impairments in the context of AD.

The fact that AD patients show an increased risk in seizures (Amatniek et al., 2006; Born, 2015), adds another modality that influences cognition and was shown to be mediated by seizure-induced suppression of c-Fos (Corbett et al., 2017). Interestingly, AD patients do also have a higher risk of developing depression and other psychiatric disorders (Lyketsos & Olin, 2002), that might further affect cognition. How these comorbidities contribute to cognitive impairments in AD is an ongoing debate and remains to be addressed on the level of engram cells.

All these studies suggest a multi-facetted and region-dependent impairment of the engram in AD. For example, engram *interference* is pointing towards a CA1 circuit-specific impairment of memory. Similarly, the *recruitment* and *reactivation impairments* were specific to DG. In later stages of AD, memory impairment will be rather caused by the loss of neuronal and potentially engram cells. In Europe, current treatment strategies to ameliorate the cognitive impairments in AD are solely symptomatic and mostly target the cholinergic system. Whether targeting one of the above-mentioned junctions has the potential to ameliorate memory recall impairments sustainably has to be revealed.

4.2. *Rett syndrome*

Similar to what is seen in AD (section 4.1), ensemble activity in the CA1 region of the hippocampus during recall is also elevated in a mouse model of Rett syndrome (He et al., 2022) (Table 1). Rett syndrome is a neurodevelopmental disorder affecting 1 in 10.000 female births worldwide (Chahrour & Zoghbi, 2007), with an age of onset of 7–18 month (Hagberg et al., 1983). It is caused by de novo mutations in the X-linked methyl-CpG-binding protein 2 gene (MECP2) that result in diverse symptoms ranging from motor impairments and loss of language skills to deficits in the social domain. It is furthermore associated with severe dementia within 18 months from onset of the disease (Fabio et al., 2016; Hagberg et al., 1983).

A heterozygous knockout of MECP2 in mice recapitulates many symptoms of patients, including a severe learning and memory deficit (Samaco et al., 2013). This is potentially resulting from an imbalance of excitation and inhibition (Kee et al., 2018). More specifically, He et al. revealed that MECP2-negative O-LM interneurons in CA1 receive reduced input from pyramidal neurons and thus elicit less feedback inhibition onto the latter. Consequently, a larger CA1 ensemble activity could be seen via Ca^{2+} imaging. Chemogenetic silencing CA1 O-LM interneurons during contextual fear learning in healthy mice mimicked the long-term memory impairments seen in the mouse model of Rett syndrome. Vice versa, the long-term memory impairment in the model was ameliorated by chemogenetic stimulation of O-LM INs in CA1 (He et al., 2022). Under physiological conditions O-LM INs are required for contextual fear learning by filtering out the aversive sensory event to allow for the encoding of contextual information in hippocampal CA1 (Lovett-Barron et al., 2014). Here, the deficient recruitment of O-LM interneurons during contextual fear conditioning caused an elevated ensemble activity (higher number of cells showing Ca^{2+} transients) and

impaired recall.

These results suggest engram *interference* to be the underlying cellular mechanism. In line with what we know from AD, this supports the hypothesis that sparse ensemble activity in CA1 bearing mnemonic content is crucial for correct information processing and thus successful recall. Given that CA1 is thought to act as an evaluator of contextual information, comparing the past and current experience (see section 4.1), it is tempting to speculate that this function is impaired in diseases with affected O-LM function, leading to a false evaluation of an actual known and fearful conditioned context (He et al., 2022). Deep brain stimulation (DBS) of the medial septum would present a promising target, as its manipulation was shown to prevent disease-associated seizures (Takeuchi et al., 2021) and lead to cognitive improvements (He et al., 2022).

4.3. Parkinson's disease

After AD, Parkinson's disease (PD) is the most prevalent neurodegenerative disease. It is neuropathologically characterized by the presence of Lewy bodies and Lewy neurites, which consist of the α-synuclein protein (Spillantini et al., 1997). The cardinal symptomatic hallmarks of PD are tremor, rigor, bradykinesia and postural instability (Hoehn & Yahr, 1967). Besides, cognitive impairment is a common symptom (Hely et al., 2008). Memory deterioration can remain mild, but also progress to dementia which is then referred to as Parkinson's disease dementia (PDD) (Aarsland et al., 2021). If onset of dementia precedes motor symptoms or occurs within the first year of motor symptom onset, the condition is declared as dementia with Lewy bodies (DLB) (McKeith, 2000; McKeith et al., 2017). These two synucleinopathy syndromes can together be classified as Lewy body dementia (LBD) (Jellinger & Korczyn, 2018; Taylor et al., 2020).

In PD, degeneration of dopaminergic neurons is causal for the cardinal motor symptoms but the dysfunction of the dopaminergic system can also be responsible for cognitive decline (Aarsland et al., 2021; Fahn, 2008). Defective noradrenergic, GABAergic, glutamatergic and importantly cholinergic neurons (Aarsland et al., 2021; Belloso-Iguerategui et al., 2023; Huynh et al., 2021; Pasquini et al., 2021) additionally contribute to the pathology of dementia in PD (Aarsland et al., 2021). Comparison of post-mortem human brain samples from PD patients with and without dementia revealed a more severe decrease of cholinergic function as well as loss of cholinergic neurons in demented than non-demented patients (Hall et al., 2014). Of note, the disruption of the cholinergic system was shown to be region specific rather than global. This is in line with multiple positron emission topography - and magnetic resonance (MRI) studies (Aarsland et al., 2021; Bohnen et al., 2006; Kanel et al., 2020; Pereira et al., 2020). For example, a nuclear group of the cholinergic system, the nucleus basalis of Meynert, seems to play a key role in cognitive decline as its degeneration is predictive for the degree of mnemonic deficits in LBD patients (Kanel et al., 2020; Pereira et al., 2020). As mentioned above, the dysfunction of the cholinergic system is also known to contribute to cognitive deficits in AD (section 4.1). Moreover, in some cases of LBD the amyloid and tau pathology are co-occurring with α-synuclein deposits (Irwin et al., 2013). It could therefore be hypothesized that similar mechanisms of engram malfunction are present in both neurodegenerative diseases. For example, the reduced cholinergic input in hippocampal CA1, resulting in a dysfunction of SST-expressing O-LM interneurons (Schmid et al., 2016), potentially leading to engram *interference* **(**Fig. 2**).**

Besides, the overall cell loss might contribute to memory deterioration as it is probable that the degenerating cells include engram cells which carry mnemonic information **(**Fig. 2**).** Increasing prevalence of dementia over the course of the disease (Aarsland et al., 2021) seems to support a causal relationship between *neuronal loss* and memory impairment. However, it is important to mention that cognitive decline can already be seen during early stages of the disease, where neuronal loss is less prevalent (Belloso-Iguerategui et al., 2023). Recently, Belloso-Iguerategui et al. hypothesized that preceding neuronal loss, synaptic dysfunction causes cognitive deficits. In a rat model of PD, they identified differentially expressed genes associated to synaptic functions as well as impaired chemically induced long-term potentiation (cLTP) already in the earliest stage of the model disease.

Even though cognitive decline starts to be examined more thoroughly in animal models of PD (Haikal et al., 2024), the exact engram mechanisms leading to impaired memory are still unclear and to our knowledge no studies examining engrams in PD models were conducted to date (Aarsland et al., 2021; Haikal et al., 2024). Therapeutic approaches of dementia symptoms in PD mostly target the cholinergic system and are similar to those recommended in AD (Reingold et al., 2007). The different neuropathological hallmarks as well as efficacy of treatments, however, underline differences of the pathologies and the need for further research.

4.4. Fragile X syndrome

Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by a loss of function mutation in the fragile X mental retardation (*FMR1*) gene which encodes the fragile x mental retardation protein (FMRP) (Fu et al., 1991; Hagerman et al., 2017; Verkerk et al., 1991). Along with different strongly altered physical features, FXS is associated with intellectual disability, attention deficit hyperactivity disorder (ADHD) and syndromic autism spectrum disorders (ASDs). Cognitive deficits, including memory impairment, are key features observed in FXS patients (Hagerman et al., 2017) with an incidence of dementia of nearly 10% in patients over the age of 40 years (Sauna-Aho et al., 2018; Utari et al., 2010).

In an animal model of FXS, it was shown that normal expression of FMRP in hippocampal CA1 is required for contextual memory formation. The extent of overlapping cells active during both learning and recall was decreased in *FMR1* knock-out (KO), compared to wildtype mice. This was not due to an overall reduced number of cells active during learning and recall as it was shown to remain the same in *FMR1* KO compared to wildtype mice (Li et al., 2020) (Table 1). This suggests a preferential *reactivation impairment* in the KO mouse model to be responsible for the memory impairment. This is further supported by the positive correlation between the reactivation efficacy of the learning induced CA1 engram cells and the behavior in a contextual fear memory task (Li et al., 2020) **(**Fig. 2**).**

The underlying molecular mechanisms might lie in compromised plasticity-related changes: As an RNA-binding protein, FMRP interacts and regulates translation of a large number of mRNAs and synthesis of many synaptic plasticity related proteins (Darnell & Klann, 2013). These alterations are potentially contributing to reduced network connectivity and memory consolidation. Exposure to enriched environment (EE) can rescue fear memory recall and engram reactivation in *Fmr1* KO mice (Li et al., 2020). EE ameliorates the memory deficit through different proposed mechanisms, such as enhanced neurogenesis (Kempermann et al., 1997), increased dendritic density and complexity (Faherty et al., 2003), changes in synaptic protein expression (Hüttenrauch et al., 2016; Nithianantharajah & Hannan, 2006) and neurotrophic factors (Bekinschtein et al., 2011). EE can also alter the plasticity threshold (LTP) in the hippocampus and thus alter the Hebbian plasticity induction rules supporting memory engram formation (Artola et al., 2006; Duffy et al., 2001; Hsu et al., 2019).

Engram studies in different forms of dementia revealed divergent but overlapping mechanisms of engram impairment. While some mechanisms remain speculative, it was shown that the etiologically dissimilar diseases AD (section 4.1) and Rett syndrome (section 4.2) seem to share their mechanism of engram impairment, namely *interference*. Potentially, by acting on the same cellular entities, i.e. SST-expressing O-LM interneurons in hippocampal CA1. In later stages of neurodegenerative diseases, like AD and PD (section 4.3), *neuronal loss* is further contributing to the impairment of memory. However, the precise consequences

of neurodegeneration on the engram level are yet to be revealed. As multiple vulnerable entities are reported for AD, the disease comprises several mechanisms of engram impairment that suggest a regional-dependency and might also change with disease stage. Thus, mechanisms of engram malfunctioning were found to co-act within diseases.

5. Epilepsy

"Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures(…)" (Fisher et al., 2014). Seizures are paroxysmal episodes characterized by transient behavioral (motor, sensory, psychiatric) changes resulting from aberrant synchronous neural activity spreading across one or more brain circuits (Devinsky et al., 2018; Fisher et al., 2014; Kanner & Bicchi, 2022). Focal epilepsies, including temporal lobe epilepsy (TLE) and frontal lobe epilepsy (FLE), are among the most frequently occurring forms of epilepsy (Wirrell et al., 2011). Cognitive deficits associated with epilepsy include both long-term and short-term memory impairments. TLE is linked to both long-term episodic and semantic memory deficits (Barrett Jones et al., 2022). In contrast, FLE is primarily associated with working memory impairments (Centeno et al., 2010). In this review, we categorize mechanisms contributing to engram dysfunction, as an underlying cause of epilepsy associated memory impairments, into four distinct groups: *neuronal loss*, *impaired reactivation, recruitment impairment* and *pathological association* **(**Fig. 2**).**

Neuronal loss induced memory impairment is widely reported in classic TLE and TLE with hippocampal sclerosis affecting episodic and everyday memory, amongst others (Rzezak et al., 2017). In a rodent model of TLE, decreased neuronal density in the dentate gyrus, entorhinal cortex and in CA1 has been reported (Du et al., 1995; Schwarcz & Witter, 2002). Furthermore, in a rare subtype of TLE, called transient epileptic amnesia (TEA), memory impairments were shown to be highly correlated with hippocampal atrophy, indicating *neuronal loss*, and potentially engram cell loss, to be responsible for these deficits (Butler et al., 2009; Fitzgerald et al., 2013).

In contrast, *impaired reactivation* is a mechanism that has been described independent of *neuronal loss*. It is characterized by impaired consolidation or reconsolidation, ultimately causing memory impairment. Epilepsy associated reactivation impairments can be further classified into memory impairments due to ictal disturbances, occurring during seizures, and inter-ictal disturbances, occurring in between seizures. During epileptic seizures impaired consolidation can directly affect the memory engram, thereby causing a *reactivation impairment*. For example, it was shown in mice that introduction of a chemically induced seizure (CIS) after learning, results in a transient decrease in performance in a spatial memory task and impaired recall on the following day (Naik et al., 2021) (Table 1). Interestingly, on a cellular level, a significant overlap between memory and seizure-activated neuronal cells in CA1 was seen. Seizures and memory processes engage similar cellular and plasticity-related mechanisms in neuronal populations in CA1. Thus, introduction of a seizure might reset the memory circuit and thereby hinder successful consolidation, leading to cognitive deficits due to a *reactivation impairment*. Another hypothesis includes the actions of chronic seizure-induced ΔFosB, a highly stable splice variant that suppresses expression of c-Fos over time and by this contributes to cognitive dysfunction (Corbett et al., 2017).

Interictal memory impairments persist in the period between seizures in the absence of an active seizure. Interictal memory disturbances in TEA is typically manifested through autobiographical amnesia (AbA), topographical amnesia (TopA) and accelerated long-term forgetting (ALF). ALF is characterized by rapid forgetting over longer time periods from days to weeks without any apparent deficit in learning or initial retention (Blake et al., 2000). ALF is mostly associated with disruptions in the neurophysiological processes or network activity involved in long-term memory consolidation whereas, AbA might result from a consolidation or reconsolidation defect (Baker et al., 2021; Blake et al., 2000; Naik et al., 2021). From a mechanistic perspective, these memory impairments can be attributed to epileptiform activities, abnormal brain electrical patterns, which persists during the pre-ictal or interictal periods or in the ictal period or in both (Gajic et al., 2015). For example, interictal epileptiform discharges (IED) are a type of epileptiform activity, which is linked to reduced memory performance. It was shown that IEDs induce inappropriate cortical oscillations in the medial prefrontal cortex (mPFC), resulting in memory impairment (Gelinas et al., 2016). Hippocampal – mPFC coupling through oscillations, namely ripples and spindles, is important for brain wide memory consolidation during non-rapid eye movement sleep. It is tempting to speculate that this impaired consolidation ultimately results in an *reactivation impairment* of an engram complex spanning the hippocampal-cortical network.

Seizure induced *recruitment impairment* suggests the inability of potential engram cells to take part in a memory trace due to altered coding or plasticity characteristics, which ultimately leads to a memory encoding deficit. The exact seizure-induced plasticity mechanisms contributing to memory impairment remain debatable. One hypothesis is the occurrence of LTP saturation in potential engram cells. The saturation might render the cells unfit to be recruited in a memory trace resulting in impaired spatial learning (Barnes et al., 1994; Nicoll, 2017). This is supported by the report of a single-seizure-induced dendritic spine enlargement and synaptic potentiation in CA1 cells (Naik et al., 2021). On the other hand, a decrease in hippocampal LTP induction is suggested as a potential cause of mnemonic impairments in a status epilepticus model (Suárez et al., 2012), in pilocarpine-induced seizure model (Lenz et al., 2017) and, in a PTZ-induced seizure model (Han et al., 2016; Lynch et al., 2000). Both ways of LTP perturbation might hint at a potential engram cell *recruitment impairment* as an underlying cause of memory deterioration. Even without an active seizure, encoding deficits can be manifested due to interictal disturbances. Pathological high frequency oscillations (pHFO) are frequently associated with interictal spikes. As shown in a rat model, pHFOs during active foraging can significantly reduce the number of active place cells responding to ripple-like events and reduce hippocampal theta power, resulting in a reduction of the total number of place fields. Moreover, there is a further reduction in spatial precision of place cells responding to the pHFO (Ewell et al., 2019) and thus results in a spatial memory encoding deficit via potentially rendering them ineligible to be recruited to the engram.

Apart from seeing engram malfunction in response to seizures or epileptiform activity, memory engram-like mechanisms might also play a role in the initiation of seizures. A popular hypothesis regarding ictogenesis was put forward by Goddard and Douglas in 1995. They proposed a seizure engram analogous to the physical substrate of long-term memory (Goddard & Douglas, 1975). Although in most patients, seizures occur spontaneously, in few cases, reflex epileptic seizures happen recurrently in response to specific triggers (Fisher et al., 2014; Italiano et al., 2014; Okudan & Özkara, 2018), which highly resembles context-dependent associative memory formation in classical conditioning (Dickinson, 1981; Lai et al., 2024). In a study led by Lai et al., a novel conditioned seizure memory (CSM) paradigm was developed that allowed for the pairing of seizure onset with a sensory cue. Subsequently, cue presentation reliably recalled the seizures. This was shown also across different rodent species and seizure models (Lai et al., 2024) (Table 1). Furthermore, artificial activation of the cue responsive engram cells in the DG, paired with the chemically-induced seizure, could successfully create artificial CSM. This might be indicative of a *pathological association* between the cue-responsive engram and ictogenesis.

Moreover, it was shown that an exposure to seizure memory cues triggers time-dependent molecular changes in memory-related signalling pathways, similar to those observed in reconsolidation (Lai et al., 2024). Signalling pathways implicated in memory reconsolidation include brain derived neurotrophic factor (BDNF) (Gonzalez, Radiske, et al., 2019), early growth response factor 1 (EGR1) (Gonzalez, Rossato, et al., 2019), mammalian target of rapamycin (mTOR) (Gafford et al.,

2011; Hoeffer & Klann, 2010), and extracellular signal–regulated kinase (ERK) (Atkins et al., 1998; Kelly et al., 2003). During specific time windows of reconsolidation, memories are susceptible to impairment, which offers a novel therapeutic strategy for seizure treatment. Protein synthesis is a fundamental mechanism during the reconsolidation process after memory recall (Bellfy & Kwapis, 2020; Nader, 2015; Nader et al., 2000; Tronson & Taylor, 2007). As successful reconsolidation of a CSM involves the aforementioned signalling pathways, blocking those within a limited timeline of reconsolidation provides an opportunity to attenuate CSM (Bockaert & Marin, 2015; Kukushkin et al., 2022; Lai et al., 2024; Ye et al., 2017) and thus, to eliminate the *pathological association* of seizure-memory cues and ictogenesis. For example, the introduction of the mTOR inhibitor Everolimus within 1 h of seizure activity, and therefore within the time interval of the reconsolidation window, decreases the IEDs significantly. This ultimately reduced seizure reoccurrences in patients with refractory epilepsy (Lai et al., 2024). Memory consolidation targeting strategy offers several advantages over traditional antiepileptic drugs (AEDs). As AEDs are primarily designed to alleviate seizure symptoms, it often fails to respond to memory complaints. Moreover, the CSM targeting approach works efficiently with a single dosage within the critical time window unlike AEDs, which needs to be administered on a long-term basis (Lai et al., 2024).

6. Chronic pain

According to the International Association for the Study of Pain, pain is an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). It is therefore vital and protective in acute situations, but tremendously lowers the quality of life in case of pathological chronicity. Chronic pain is a major health problem, being one of the leading causes of disease burden worldwide (Cohen et al., 2021). Although being described as a purely somatic process before, the understanding of pain perception has changed over the last decades to a multidimensional dynamic also taking psychosocial factors into account (Engel, 1977; Meints & Edwards, 2018; Prakash & Golwala, 2011). A wealth of experimental investigations pinpoint to the role of central circuits e.g. limbic circuits which modulate the experience of pain (Kuner & Kuner, 2021). Patients experiencing pain even without any preceding somatic damage further support the hypothesis of a pivotal role of central dysregulation (Fitzcharles et al., 2021; Kosek et al., 2016; Taylor et al., 2021). One aspect that potentially modulates the experience of pain is memory, however, how and to which extent is still not clear. On a macroscopic level, functional neuroimaging revealed multiple prominently active brain regions during the experience of chronic pain. Compared to findings in acute pain, it seems that under chronic pain conditions specific structures of the limbic system show higher activity, rather than a general hyperactivity of brain regions. This supports the hypothetical importance of emotional factors in developing chronicity of pain (Apkarian et al., 2011; Prakash & Golwala, 2011).

For investigating the emotional aspect of chronic pain, Corder et al. tagged an engram in the basolateral amygdala (BLA). This engram accounts for the unpleasantness, but not the sensory discrimination of the pain experience in nerve-injured mice, showing signs of hyperalgesia, exacerbated pain percept, and allodynia, i.e. pain percept in response to innocuous stimuli (Corder et al., 2019) (Table 1). Pain stimuli of different modalities, namely mechanical stimuli, cold and hot temperature, all led to a significant rise of activity in the examined brain region. During light touch, the number of active BLA neurons in injured animals was strongly increased compared to healthy controls, suggesting that the BLA plays an important role in the emergence of allodynia in chronic pain (Corder et al., 2019). Silencing these neurons did not alter reflexive behavior, indicating the intact processing of sensory information, but led to a decrease in affective-motivational behavior, measured by the avoidance of the presented stimuli (Corder et al., 2019). Without the affective component of pain, learning to avoid potentially harmful stimuli is not possible, whereas an overrepresentation and thus, *over encoding* of the negative valence of stimuli might contribute to the disproportionate experience of pain. From an engram perspective, this study supports the hypothesis of an increased allocation of neurons to an engram, which can be termed as *over encoding* **(**Fig. 2**)**.

Recently, Stegemann and colleagues extended the understanding of circuits mediating affective components of pain by investigating long-term fear memory engrams and their influence on the percept of pain. Fear encoding ensembles were captured in the prefrontal cortex of mice using a TetTag System. A fluorescent marker visualized potentially participating neurons, whereas photoactivatable ion channels allowed for the manipulation of those cells. To investigate the influence of fear of pain on symptoms of chronic pain, a contextual fear conditioning (cFC) paradigm was used. Interestingly, the experience of cFC alone was not enough to induce symptoms of chronic pain, but was shown to enhance hyperalgesia and allodynia in mice displaying the model disease, suggesting a 'second hit' mechanism. In line with this, optogenetically silencing the fear of pain engram alleviates symptoms of chronic pain. Cellular investigation revealed a greater overlap of engrams active during fear and hyperalgesia or allodynia compared to healthy controls (Stegemann et al., 2023) (Table 1). We speculate that constant experience of pain due to the model disease leads to the formation of *pathological associations* with the fear experience and therefore to an engram that increasingly interacts with the pain engram arising in response to the painfully experienced stimuli **(**Fig. 2**)**. In line with the neuroimaging data in humans, these engram studies indicate an enhanced negative valence of pain under pathological conditions. In addition, the chronic aversive experience of pain could further lead to *pathological associations* with environments that were neutral before **(**Fig. 2**)**. Consequently, the exposure to the now negatively connotated contexts might make forgetting of the pain memory more difficult (Apkarian et al., 2011).

7. Psychiatric disorders and their mnemonic burden

7.1. Major depressive disorder (MDD)

Psychiatric disorders such as anxiety, major depressive disorder (MDD) and schizophrenia are affecting hundreds of millions of people world-wide, with often poorly defined etiologic origins (Hollander et al., 2020). Cognitive impairment is a common symptom that accompanies many psychiatric diseases, with MDD presenting one of the most common. MDD is a multifactorial disorder, affecting more than 250 million people worldwide (Mental disorders GBD 2019 Mental Disorders Collaborators, 2022; Murray & Collaborators, 2024). The fundamental symptoms are a depressed mood and anhedonia, the reduced ability to experience pleasure. They are often accompanied by other symptoms including feeling of worthlessness, fatigue as well as cognitive symptoms (Malhi & Mann, 2018). The cause of MDD is believed to be strongly coupled to environmental risk factors interacting with a probable, yet not clearly defined genetic component, and often occurring with different comorbidities (Flint, 2023).

From all environmental risk factors chronic stress presents the most influential one with proven causal relation to the onset of MDD (Richter-Levin & Xu, 2018). Stress might indeed also present the mechanistic link between MDD symptoms and cognitive impairment. For example, a common mouse model was developed based on the fact that chronic social stress induces depression-like symptoms in mice, called the chronic social defeat stress (CSDS) model (Kudryavtseva et al., 1991). Interestingly, the CSDS protocol induces depression-like symptoms only in a subset of susceptible mice, whereas some mice reveal to be resilient to stress (Krishnan et al., 2007). A recent review article hypothesized three mechanisms by which stress induces memory impairments in the context of depression: by (1) suppressing hippocampal neurogenesis, (2) inhibiting dopamine neurons and (3) sensitizing the amygdala (Dillon & Pizzagalli, 2018); mechanisms that have also been associated to act on

engram cells, e.g. by a reduced recruitment of immature neurons in neurogenesis-impaired AD mice.

Memory impairment is usually not seen as a core symptom of MDD, but is believed to be critically involved in the negative sense of self, the world and the future that is characteristic for the disease, according to Beck's cognitive triade (Beck, 1967). Depressive individuals suffer from poor memory of positive experiences and a bias towards negative experiences. Moreover, recollection is impaired (Dillon & Pizzagalli, 2018; MacQueen et al., 2002). A hyperactive amygdala during negative memory recall in depressed patients may account for a bias towards negative memories (Young et al., 2016). In contrast, positive recall was associated with reduced amygdala activity. On the level of engrams this would imply a dominance of engrams with negative valence which generalize over experiences. Indeed, it was found that cognitive symptoms of depression are associated with enhanced reactivation of negative engrams in the hippocampus (Zhang et al., 2019) (Table 1). On the cellular level it was shown that negative thinking induced lasting cellular and behavioral abnormalities, as mimicked by chronically activating a negative engram in the ventral hippocampus (Jellinger et al., 2024) (Table 1). These facts let us to identify *pathological associations* as one mechanistic aspect of engram impairment in MDD (Fig. 2).

Moreover, depression is linked to reduced hippocampal volumes (Bremner et al., 2000; Sheline et al., 1996), mainly due to grey matter reduction in the hippocampus. Furthermore, impaired neurogenesis and gray matter reduction in cortical areas, especially the prefrontal cortex is reported (Marx et al., 2023). These findings might account for memory impairments due to *neuronal loss* (Fig. 2) and potentially associated engram cell loss. Reduced neurogenesis, might lead to *impaired recruitment* of engram cells, similar to the findings in AD (Fig. 2) (Dillon & Pizzagalli, 2018; Krishnan et al., 2007; Kudryavtseva et al., 1991; Richter-Levin & Xu, 2018). How can engram manipulation counteract these impairments? It was demonstrated that activating an engram coupled to a positive experience is sufficient to suppress depression-like behavior (Ramirez et al., 2015) (Table 1). By chronically activating the positive engram, the anxiolytic effect was shown to be long-lasting, i.e. observable beyond acute activation and ameliorate impairments of neurogenesis. Current antidepressant therapeutics are believed to induce neurogenesis (Boldrini et al., 2013; Santarelli et al., 2003) and therefore, also ameliorate symptoms on that level.

7.2. Post-traumatic stress disorder (PTSD)

Posttraumatic stress disorder (PTSD) is a devastating psychiatric disorder with a lifetime prevalence of 4 % (Koenen et al., 2017). It is believed that the traumatic experience is "over-encoded" in a neuronal ensemble. One possible mechanism involves the action of growth hormones that induced an increased allocation of neurons in the amygdala while encoding a negative experience (Gisabella et al., 2016) (Table 1). Depleting the growth hormone receptor in SST neurons, reduces fear in mice, suggesting an involvement of inhibitory neurons (Dos Santos et al., 2023). Thus, the mechanism of *over encoding* implies an increased number of neurons participating during initial encoding and possibly during recall, both potentially causing a mental dominance of the respective memory (Fig. 2).

Moreover, it was shown that the valence of a contextual engram can be switched artificially in DG, but not BLA, meaning that the contextual scaffold encoded in the hippocampus is associated to malleable emotions (Redondo et al., 2014) (Table 1), suggesting a *pathological association* (Fig. 2). If this traumatic engram can be retrieved by parts of the initial traumatic experience, it can be made accessible for manipulation strategies. Tagging the negative engram during the traumatic experience will then make it possible to switch its valence to be neutral, in a similar approach than Redondo et al. achieved it. Considering prospective translational aspects, tagging of engrams during the initial traumatic experience cannot be achieved. An interesting study by Khalaf et al., however, tagged the engram during the recall session and by this was able to facilitate remote fear memory attenuation, while activating the recall ensemble during the extinction process (Khalaf et al., 2018) (Table 1). Vice versa, inactivating the recall ensemble impaired the attenuation process. This strongly argues for the engram to be bound to the negative emotion in a way that it has to be reconsolidated to achieve a neutralization of the engram-associated valence. In animal models this neutralization can be induced by chemo- or optogenetic reactivation of the engram, as well as by natural recall, paired with the artificial activation of a positive engram: optogenetic activation of a positive memory in a fear conditioned context led to a reconsolidation of the fearful memory and thus, fast extinction (Grella et al., 2022) (Table 1). In humans, fMRI neurofeedback training to downregulate amygdala activity while recalling traumatic episodes is just one of several promising non-invasive therapeutic approaches (Zhao et al., 2023).

7.3. Addiction

Addiction or substance use disorder is a chronic, relapsing disorder with a complex etiology that affects 2.2 % of people worldwide (Castaldelli-Maia & Bhugra, 2022). Drug abuse is known to cause strong, long-lasting memories of context-drug effect associations, characterizing addiction as a disorder of learning and memory (Whitaker & Hope, 2018). The causal role for c-Fos-expressing neuronal populations to express a learned behavior related to diverse drugs (e.g. heroin, cocaine, alcohol, etc.) has been revealed for different pre-frontal cortex areas, nucleus accumbens, striatum, and amygdala (Whitaker & Hope, 2018). However, the exact role of different brain regions in encoding drug-related information and associations has still to be revealed. It has been postulated that the robust imprint of drug exposure onto brain function relies on the ability of neuronal plasticity mechanisms to react to a given stimulus in order to modulate the response of brain networks (Salery et al., 2021). For example, the allocation of lateral amygdala neurons to a cocaine engram was shown to be CREB-dependent (Hsiang et al., 2014).

The first brain region that was causally linked to drug-induced behavior (specifically: locomotor activity) beyond observational studies, was the nucleus accumbens (NAc). In a first step, the neuronal population that was engaged during drug administration in a specific context was tagged. For targeting the specific neuronal population β-galactosidase was expressed in transgenic animals in a *c-fos* promoter-dependent manner. By intracranial injection of the prodrug Daun02, it was possible to ablate neurons that contain β-galactosidase, as this converts Daun02 to the neurotoxic drug daunorubicin. Excitingly, inactivating this engram could reduce drug-induced locomotor activity (Koya et al., 2009; Koya et al., 2016) (Table 1). It was further shown that the environmental context activated specific, sparsely distributed c-Fos-expressing neurons in the nucleus accumbens that mediate drug-seeking behavior. To probe the drug-associated context memory in rodents the conditioned place preference (CPP) test is a commonly used paradigm. Here, a drug-reward is repetitively given at a specific location within an environment. Once the mice are placed back into that environment, they will prefer the location associated to the previous drug administration, which can be quantified by their time spent in that part of the environment. One study by Zhou et al. tagged engram cells in ventral CA1 and the NAc during CPP training. Ventral CA1 engram cells were shown to preferentially connect to NAc and by this mediate memory recall. NAc engram cell activation alone was shown to be sufficient for mice to prefer the location they have been receiving the drug, despite inhibition of the ventral CA1 (Zhou et al., 2019) (Table 1). These data suggest that the mechanism of engram malfunction is the *pathological association* between the drug of abuse and the environmental context the intake took place, including associated cues (Fig. 2).

Of note, this engram-centric description of neural correlates of maladaptive behavior neglects the complex etiology and varying predispositions that people suffering from addiction hold. There are several concepts for therapeutic approaches to tackle addiction that act on the

cellular domain. One idea is to enhance neurogenesis with the aim to accelerate forgetting in the context of substance abuse disorder, but also PTSD (Fujikawa et al., 2024). For targeting drug-related cells directly, it is crucial to clarify whether drugs engage the same neuronal ensembles that are used by non-drug rewards (e.g. food) (Cruz et al., 2015). The seeking for drug vs. natural rewards was shown to be mediated by a largely overlapping population of neurons in the infralimbic cortex, with only a few neurons responding specifically to either the drug or the natural reward (Pfarr et al., 2018). However, some interconnected regions become only necessary for behaviors motivated by drugs, but not natural rewards (Nall et al., 2021), opening up a potential point of entry for ensemble targeting strategies, without affecting reward processing in general. Moreover, it is important to clarify whether ensembles for learning are the same that become important for extinction. A question that needs to be addressed with respect to the specific brain region and type of drug. It was shown that drug intake and extinction cause the same activation of the mPFC, however involve separate neuronal populations that also have distinct projection targets in the NAc (Warren et al., 2019). The drug-context activated cell population was shown to be long-lasting and responsible for cue-evoked relapse and thus provides a potential target for treatment of relapse prevention (Visser et al., 2020).

The psychiatric disorders mentioned here do all share the characteristic of being associated with problematic, often persistent memories that are not prone to be forgotten (hypermnesia). Of note, these diseases are further known to be accompanied by impairments on the cognitive domain, majorly caused by stress (Girotti et al., 2024). The investigation of engram cells in this context, gave rise to discrete neuronal correlates that are causally linked to disease-associated symptoms, like anhedonia or drug-seeking behavior.

8. Cellular entities give rise to shared memory impairment mechanisms

Utilizing the concept of an engram helps to assess the integrity of memory encoding, consolidation, recall and reconsolidation. Across the diseases covered by our review article, we identified six mechanistic categories of memory malfunctioning from an engram cell-centric perspective: *neuronal loss, interference, reactivation impairment, recruitment impairment, over encoding* and *pathological associations*. These mechanisms are not mutually exclusive, might overlap and also be shared by disease stages as well as several distinct diseases. Engram cell impairment mechanisms appear to be shared by diseases regardless of their pathogenic origin, but rather depending on affected brain regions and cell types or molecular components. We hypothesize that diseases acting on the same cellular or subcellular entities in the same brain regions also share mechanisms of memory impairment. For example, AD (section 4.1) and Rett syndrome (section 4.2) do not share the same pathogenic mechanisms, however, both act, amongst others, on the integrity of hippocampal SST-expressing O-LM interneurons, thereby altering local microcircuits that potentially impact engram accessibility. We further distinguish mnemonic malfunction based on its manifestation as either, an impairment of memory (amnesia) or a prolonged maintenance of a memory (hypermnesia) (Fig. 2). We suggest *neuronal loss*, *interference, reactivation impairment* and *recruitment* impairment as main mechanistic groups across diseases accompanied by amnesia. Conversely, we propose *over encoding* and *pathological associations* as mechanisms associated with hypermnesia.

Neuronal loss presents the irreversible end point of a complex spectrum of possible memory impairments among diseases associated with amnesia (Ryan & Frankland, 2022). To our knowledge, this has not been investigated on an engram level. Depending on the magnitude, neuronal loss might affect memory by the loss of engram cells or by impacting the overall integrity of a specific brain region. Both might be relevant in neurodegenerative diseases, like AD (section 4.1) and PD (section 4.3), but also for subtypes of Epilepsy (section 5) and MDD (section 7.1), which are associated with hippocampal sclerosis (Rzezak et al., 2017) and a reduced hippocampal volume (Bremner et al., 2000; Sheline et al., 1996), respectively. Whether or not disease-caused neuronal loss affects memory by the loss of engram cells might also depend on the temporal aspect of the loss event, as slow degradation might allow for compensatory mechanisms. Given that the time point of successful intervention is mostly missed at the stage of neuronal loss, it is of major interest to treat memory dysfunction at earlier disease stages.

Engram *interference* describes an interfering cellular population that renders a reactivated engram inaccessible and consequently, leads to impaired memory recall. So far, causality was just revealed for the hippocampus (Autore et al., 2023; Poll et al., 2020), suggesting a region-specificity that is tight to hippocampal function. However, we are not excluding that interference exists elsewhere (Wimber et al., 2015). Based on existing studies in the hippocampus of rodents, we believe that the interfering ensemble arose as a natural response to the detection of environmental novelty, occurring after hippocampal internal (CA3) and external (EC) inputs to CA1 were compared and evaluated to mismatch. This is e.g. the case if a healthy mouse explores an environment which is similar (e.g. in shape) to a familiar one, but nevertheless distinct enough to violate expectations and thus, being perceived as novel. It is tempting to speculate that a diseased mouse might have narrower expectations (e.g. due to poor memory on contextual details) and thus, is more likely to experience expectation mismatches. These mismatches are associated with poor memory performance (AD, section 4.1). Mechanistically, an expectation mismatch will elicit an interfering ensemble in CA1 that on the one hand, impairs the recall of a previously encountered similar context, and on the other hand, allows for encoding of new information. As for some cases in LBD (PD, section 4.3) α-synuclein deposits are co-occurring with an amyloid pathology (Irwin et al., 2013), one could speculate that this will also lead to shared mechanisms of engram dysfunction, i.e. *interference*. In the context of Rett Syndrome (section 4.2), deficits in SST-expressing O-LM interneurons are causally linked to the occurrence of higher ensemble activity in CA1 (He et al., 2022). It has to be revealed whether this can just be observed on the level of Ca^{2+} activity, or as well on the level of c-Fos expression, as shown in AD (Poll et al., 2020). Moreover, a recent study suggests the causal involvement of local VIP-expressing interneurons in detecting novelty and disinhibiting hippocampal CA1 (Tamboli et al., 2024). Interestingly, competing engrams have been shown to cause retroactive interference in DG (Autore et al., 2023), a mechanism hypothesized to mediate forgetting in our everyday life.

Impaired reactivation of engram cells either originates from defective learning-associated subcellular plasticity and/or incomplete consolidation, e.g. by the loss of fragile x mental retardation protein (Fragile X Syndrome, section 4.4). However, it might also be caused by faulty reconsolidation, e.g. in seizure-associated amnesia (Epilepsy, section 5). These alterations would result in “normal” engram cell recruitment during learning, but subsequently impact memory storage and thus, lead to a reduced reactivation of engram cells upon recall, resulting in impaired memory. Reactivation of potential engram cells is often addressed by quantifying the overlap of neurons tagged during learning and those that show IEG-expression upon recall. The extent of overlap underlies an enormous variation depending e.g. on the temporal resolution of the method (Engram tagging strategies, section 3) and the brain region investigated. Both aspects have to be considered, when investigating reactivation. In AD, a reactivation impairment was shown for DG, but not CA1 (Table 1) and thus, might also depend on specific local microcircuits (section 4.1).

A *recruitment impairment* is, in contrast to neuronal loss, the earliest visible mechanism of engram cell impairment and manifests in a reduced number of recruited neurons to the engram. For example, there is evidence for a reduced recruitment of immature DG neurons in a mouse model of AD (section 4.1) due to reduced neurogenesis (Mishra et al., 2022). This mechanism might also affect memory in MDD (Marx et al., 2023) (section 7.1). In Epilepsy (section 5), however, it is hypothesized that a seizure-associated saturation of cellular plasticity

mechanisms (Barnes et al., 1994; Nicoll, 2017) might cause a reduced availability of neurons to be allocated to an engram.

Over encoding results from an initial "over recruitment" of engram cells during learning and manifests itself in a higher engram cell density and thus potentially dominant memory associated with a negative valence. Over encoding was shown to be induced by the presence of growth hormone in the context of fear induced stress (Gisabella et al., 2016) (PTSD, section 7.2), but might also be caused by increased excitability (Yiu et al., 2014). Whether a higher recruitment of cells to the engram also causes a preferential reactivation and whether this is causal to anxiety-related symptoms in psychiatric disorders, like MDD (section 7.1), is to be determined. In chronic pain (section 6), more BLA neurons get recruited upon light touch, than in the healthy condition (Corder et al., 2019). Hence, an increased number of neurons encoding the negative valence of stimuli might contribute to the disproportionate experience of pain.

Pathological Associations are formed if a disease-related event is paired and thus, associated with a co-occurring neutral event. Analogue to classical conditioning this leads to a conditioned reaction (Lechner & Byrne, 1998; Takehara-Nishiuchi, 2022), i.e. a pathological body reaction. Based on our engram study research, we found *pathological associations* to play a role in in reflex epileptic seizures (section 4), chronic pain (section 5), MDD (section 7.1), PTSD (section 7.2) and addiction (section 7.3). In reflex epileptic seizures, association of seizure onset and sensory cues allowed for the induction of seizures by the natural or artificial activation of the cue responsive engram alone (Lai et al., 2024). We further identified the same mechanism to be relevant in chronic pain. Lasting experience of pain may lead to the formation of *pathological associations* with the neutral environment (Apkarian et al., 2011). Additionally, the experience of fear seems to aggravate the clinical symptoms of chronic pain due to increasingly interacting fear and pain engrams (Stegemann et al., 2023). Furthermore, *pathological associations* are suggested to underly psychiatric disorders. In MDD an over-proportionate activation of negative engrams in the hippocampus was shown (Zhang et al., 2019). Presumedly, constant association with the individuals' environment increases the risk of persisting predominant negative thoughts. Similarly, patients who suffer from PTSD experience great distress by intrusive memories of the traumatic event. The over-proportionate experience of fear can be triggered by parts of the environmental context of the traumatic experience. Here two engram malfunction mechanisms are putatively mutually reinforcing, namely *pathological associations* and *over encoding*. Examining the behavior of addicted mice revealed that activating neurons encoding locomotor activity was sufficient to induce drug seeking behavior even during recall suppression of the drug intake memory (Zhou et al., 2019).

What all mechanisms have in common is their inherent natural occurrence in physiological processes. With regard to amnesia mechanisms, n*euronal loss*, although mild, is observed during healthy aging in humans (Yankner et al., 2008). Neurogenesis underlies an age-dependent decline as well (Apple et al., 2017), which represents one possibility for an *recruitment impairment.* Engram *interference* is seen in mice exploring a novel context, leading to the suppression of similar context memories and thus, allow for encoding new experiences (Trouche et al., 2016). Impaired, i.e. *reduced reactivation* is seen during natural forgetting of seemingly irrelevant information (O'Leary et al., 2024) and if memory acquisition happened under unfavorable conditions (Leake et al., 2021). Respecting hypermnesia, it is well known that strong positive or negative experiences create so-called flashbulb-memories (Diamond et al., 2007), i.e. vividly retrievable short episodic memories. It will be interesting to elucidate whether these might also underly engram *over encoding* and thus, account for the biased recall of strong memories, may they be negative or positive. Similarly, increased activation of specific brain regions can be controlled by neuromodulators, depending on the internal state (Flavell et al., 2022; Lee & Dan, 2012), which might contribute to *over encoding*. Finally, *pathological associations* can also be seen in the light of healthy associations that facilitate survival (e.g. food locations or places of detected threat). We believe that diseases hijack these mechanisms by acting on one or several components of the circuit to then cause memory malfunctioning. The causal role of the occurring memory malfunction-associated pattern mostly lies in an altered engram cell plasticity (Ryan & Frankland, 2022).

9. Translation – Challenges and chances of therapeutic approaches

Cognitive impairment can already be therapeutically targeted, for example by current pharmacological treatment strategies, e.g. cholinesterase inhibition in AD (section 4.1). Furthermore, there are long established non-pharmocological, non-invasive therapeutic options, which mechanisms stayed elusive on a cellular level so far but are thought be mediated by central processes. This includes immune conditioning (Hadamitzky et al., 2020; Lückemann et al., 2021), neurocognitive rehabilitation (Crosson et al., 2017) or psychotherapy. Bedside to bench research, referred to as reverse translation, could help to explain the success of established therapies. Conversely, translating engram knowledge from bench to bedside might pave the path to new therapeutic approaches. Unequivocally, this comes with some obstacles. Considering the challenges in non-human animals to tag and manipulate engrams despite established tools, it is a valid question to which extent results from basic research will be translatable to the clinic in the foreseeable future.

Identifying engram cells in humans is the first step to investigate the valence of engram cell populations as building blocks of memories in our species. Neuroimaging techniques such as FMRI, PET, MEG and extracranial EEG studies have led to important insights into brain activity on a regional level in humans (Klimesch, 1999; Kunz et al., 2018; Landau et al., 2011; Willems & Henke, 2021). While providing the possibility to study the whole brain in a non-invasive way, the spatial resolution of the afore mentioned methods is poor, comprising the summed activity of thousands to millions of cells. In contrast, invasive recording techniques such as intracranial EEGs (iEEG) using surface and depth electrodes, provide an enhanced spatial and temporal resolution up to single neuronal spiking. The insertion of electrodes in the human brain is done regularly in a clinical setting, including (1) deep brain stimulation (DBS) electrodes, mostly applied in the treatment of PD symptoms, and (2) depth electrodes, usually used to locate the focus of seizure onset in patients of intractable epilepsy. Depth electrodes allow the recording of local field potentials (LFP), electrophysiological recordings from proximal simultaneously active synapses, also in deep brain regions that are not accessible by extracranial EEG (Neumann et al., 2023). Moreover, a combination of intracranial macro- and microelectrodes recordings followed by detailed data analysis can be used to achieve single cell resolution (Rey et al., 2015). However, the number of simultaneously recorded neurons as well as the comparably small assessed area limits these methods. Furthermore, keeping track of a single neuron over a period of time remains challenging but would be necessary to examine long-term memory on a cellular level (Niediek et al., 2016; Quian Quiroga, 2019). In conclusion, brain-wide activity studies with a high spatial and temporal resolution are not yet provided. Of note, human engrams can currently only be studied through observational methods. While it is possible in rodents to conduct engram gain- and loss-of-function studies, sufficiency and necessity respectively cannot be investigated in our species to date. Taken together, with the aforementioned limitations scientists are cautious to interpret their findings in regard to engrams. However, multiple observational studies gathered data that meet several engram criteria (excluding sufficiency and necessity) and by this, support the hypothesis of the existence of engrams in humans. For example, similar neural activity patterns at encoding and successful retrieval of a memory were shown using fMRI and iEEG. On a single neuronal level, it was shown that reactivation of specific cells occurs during recall, which are potentially part of an engram (Gelbard-

Sagiv et al., 2008). Moreover, it was reported that reoccurrence of activated engrams happens spontaneously during awake, post learning periods, which is predictive of subsequent memory (Staresina et al., 2013). Besides studies with single-cell resolution, there are approaches that interpret less spatially resolved fMRI data in the light of engram activity (Brodt et al., 2018; Kunz et al., 2018). These measured functional changes in the so-called brain microstructure can be recorded by diffusion-weighted MRI and are suggested to be predictive of experience-dependent plasticity processes. Due to current methodological limitations, microstructure activity cannot sufficiently be attributed to engram activity. However, the measurement of microstructure activity is suggested to reflect some basal criteria of engram characteristics, e.g. the relation to a specific experience and the ability to stay dormant. It is surely interesting to answer the question of how data of different readouts and across scales align in a meaningful way. Similar to the spatially highly resolved data in rodents, bridging scales presents a major challenge in the engram field and has the potential to push engram research to the next level. We mentioned earlier that studies that proof the sufficiency and necessity of engram cells in humans are currently not actionable, due to their invasive nature, amongst other factors. It was demonstrated though, that stimulating specific brain regions leads to recall of memories associated with the activity of this exact brain regions, which was corroborated by the patient's response (Jacobs et al., 2012). This suggests that electric stimulation recreated the same activity patterns that are evoked during natural recall and supports the view that the criterion of sufficiency can in principle be investigated in humans, although not yet on the single cell level. Moreover, this also highlights the advantage that humans are able to report their free recall of a memory, which will facilitate the validation of engram manipulation strategies.

Assumed that future studies provide further support for cellular engrams as functional building blocks of human memory, the next step would be to find suitable approaches to target engram complexes in humans. For this we identify three main challenges: (1) identifying targets within an engram complex, (2) establish suitable targeting methods and (3) knowing the stability (due date) and relevance of an engram for a specific memory. These challenges are interdependent and thus, demand to be approached in a holistic manner. Identification of target regions containing potential engrams might be eased by the fact that engrams are brain wide. Mapping an engram complex of a contextual memory across brain regions has identified multiple different brain regions with varying probabilities of containing engram cells (Roy et al., 2022). The distributed nature of an engram complex suggests that memory engrams within a specific brain region may contribute to specific aspects of the total memory information. For example, dorsal hippocampal engrams are important for encoding contextual or spatial information (Pettit et al., 2022), whereas ventral hippocampal engrams are involved in social memory (Okuyama et al., 2016). Superficial brain regions, like major parts of the cortex, are technically easier to access. Supposed that engram cells in designated cortical regions have the same relevance for a given memory as other, less accessible engram cells within an engram complex, facilitates target identification. In mice, it was demonstrated that manipulating a hippocampal engram influenced activity patterns in downstream cortical brain region (Tanaka et al., 2014). Further research aiming at characterizing the significance of individual region-specific engrams among an engram complex for the evocation of a memory is needed to decipher points of entry for engram manipulation strategies. To target engram cells by IEG-dependent tagging would, at least to some extent, imply genetic manipulation. Progress in the field of adeno-associated virus-based methods to deliver genetic material into the brain by systemic injections (Chan et al., 2017; Gradinaru, 2020) reveals promising ways for future implementations. However, safety concerns and expensive development of tools have to be recognized as obstacles in the way of successful therapy introduction.

Another aspect that has to be proven is the persistence or in more practical words the "due date" of engrams. It is widely accepted that memory in general is transformed over time within and across brain regions. Hence, the question appears whether it can be trapped in an efficient and meaningful way to be manipulated for therapeutic effects. It was shown in rodents that the tagging of learning-evoked engram cells with an opsin rendered them susceptible to manipulation for at least 5 and 10 days, depending on the stability of opsin expression, among other things (Kitamura et al., 2017; Liu et al., 2012). Even if the stability of tool expression is pushed forward, there is still the question of how relevant the designated engram cells are for a remote point in time. Of note, engrams can keep or lose their relevance for recall with time and completed systems consolidation (Kitamura et al., 2017). For example, neurons in the prelimbic area of the prefrontal cortex tagged during fear conditioning or recent (1d) retrieval lose their relevance for remote (28d) recall (DeNardo et al., 2019). This was demonstrated by tagging neurons with an activating opsin, either during learning or at different retrieval sessions. Reactivating these neurons led to freezing behavior. However, the extent to which these neurons drove freezing was time-dependent, i.e. the closer the tagging was to the recall session, the more their reactivation caused freezing during remote recall. If all challenges are overcome, there is evidence that artificial engram stimulation is comparable to natural recall. For example, a study in rodents showed that the behavioral characteristics associated with an artificially and naturally evoked memory, respectively, are very similar (Park et al., 2024), which further encourages the discussion of potential translational solutions.

10. Conclusion

Engram cells revealed to be useful proxies for studying memory, under healthy as well as pathological conditions. A refinement of the current structural and functional definition of an engram may be possible by future studies that further elucidate engrams across scales and brain regions. The alignment of varying readouts across these scales (e.g. gene expression, functional and structural plasticity of synapses, neuronal firing, oscillations within and across brain regions, whole brain functional imaging approaches) will accelerate to elucidate mnemonic dysfunction on the subcellular, cellular, circuit and systems level, also in humans. We evaluated the importance of looking at engrams from the perspective of the respective brain region, as we think that the characteristics of an engram cell ensemble are tightly linked to the function of the region it is observed in. Regional variability in engram cell occurrence and characteristics is also relevant for translation, in order to make informed decisions of where to target an otherwise brain-wide engram complex.

Interestingly, we found the term "engram" not only applied to describe a neuronal population that is supposed to code for declarative, but also non-declarative memory (Eichenbaum, 2016). For example, in the context of motor behavior the term engram is used to describe the neural trace of a motor memory coding for complex actions (Hwang et al., 2022). Moreover, we found the term used independent of memory in the classical sense (Squire, 1992), e.g. to define a seizure-inducing neuronal population (section 5). Moreover, while tagging an "immunengram" during an inflammatory event, it was shown that chemogenetically reactivating the participating neuronal population led to a similar anatomically defined inflammation. The authors formulated the idea that an immunengram not only implies neurons in the CNS but further peripheral neurons, cells of the immune system and other tissue components (Koren & Rolls, 2022; Rolls, 2023). The involvement of event-specific neuronal activity prospectively allows to gain control of physiological or pathological processes, e.g. by targeting engram cells in the CNS. This presents points of intervention in the context of potential therapeutic strategies. There are also diseases that have not yet been explored from the perspective of an engram, but that hold some potential for engram-based therapeutic strategies to ameliorate memory impairments, e.g. PD (section 4.3), but also glioma, which are the most common form of primary central nervous system tumors. Glioma closely

interact with the brain tissue and vice versa (Venkataramani et al., 2019; Venkatesh et al., 2015; Venkatesh et al., 2019) and have a unique impact on the cognitive domain (van Kessel et al., 2017).

Despite their utility, we want to stress that an engram-centric description of neural correlates for maladaptive behavior neglects the complex etiology and varying predispositions that patients may hold. Thinking about engrams in a less discrete approach, turns them into our life-long companions, though transforming, interacting and constantly forming, like "dynamic quilt-like patterns specific and unique to each individual" (Gebicke-Haerter, 2014). On the one hand, the resulting unique nature of individuals' engrams makes their targeting more challenging. On the other hand, promises personalized treatment options and thus, progress in a variety of clinical fields. When discussing translation to humans and the accompanying manipulation of engrams, we shall not forget that memories are the basis of our personal identity and help us to define who we are. Considering the power of neuroscientific tools, currently utilized mostly in rodents, the question over ethical aspects of memory modification and the demand for an ethical reference frame have to be raised (Tan & Lim, 2020; Zawadzki & Adamczyk, 2021). In summary, we believe that the engram provides a feasible reference frame to answer questions concerning memory characteristics and alterations across conditions. The concept of an engram helped us already to understand the mechanistic underpinnings of mnemonic function and malfunction and will hopefully continue to be a valuable physical correlate to elucidate the extremely complex and fascinating world of memories.

CRediT authorship contribution statement

Greta Leonore Balmer: Writing – review & editing, Writing – original draft, Visualization, Investigation, Funding acquisition, Conceptualization. **Shuvrangshu Guha:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Stefanie Poll:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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