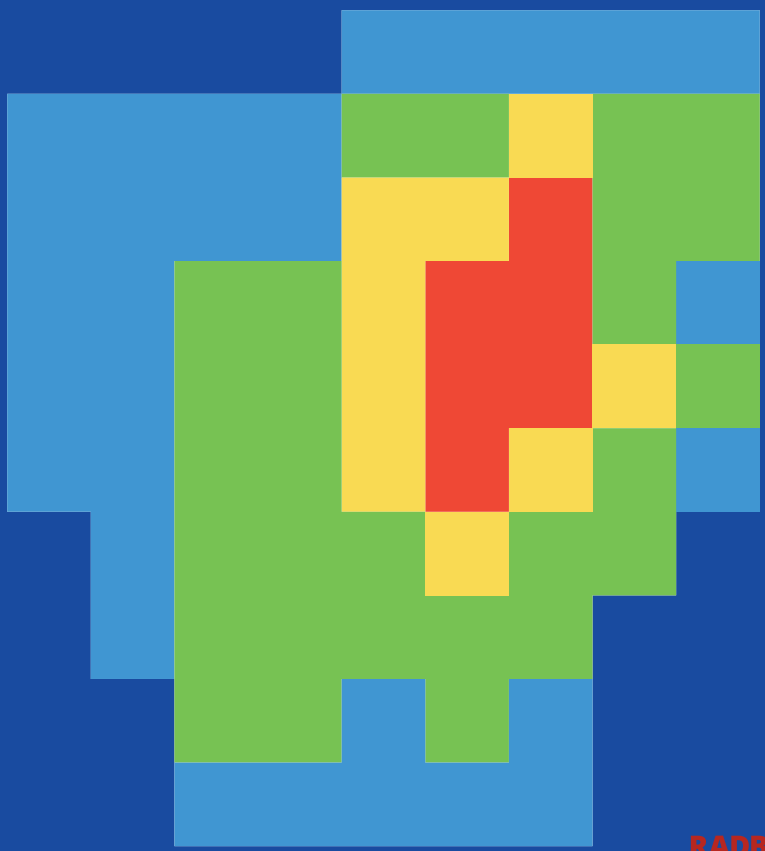
The ontogeny of hippocampal memory: Bridging behavioural and neuronal development



Juraj Bevandić

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Juraj Bevandić

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by

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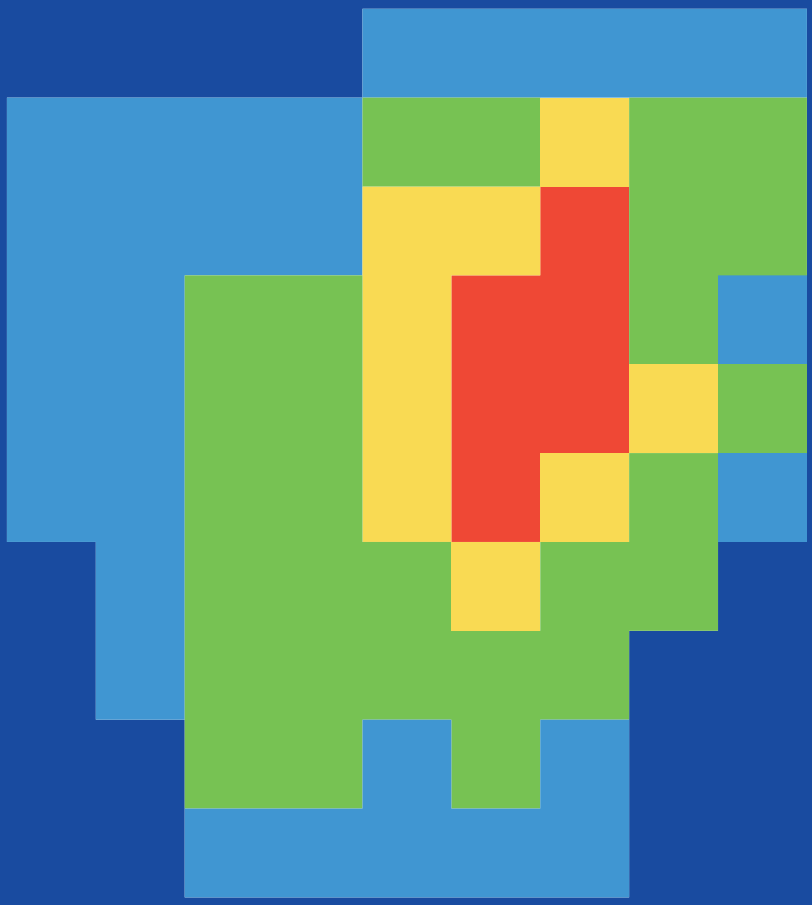


Chapter 1

General introduction

1.1 Aims of the thesis

My earliest memory is that of my mother pushing me in a stroller in our front yard. It is warm and sunny, and at some point, I must have somehow ended up on my feet or in my mother's arms because I most distinctly remember the view of my seat cushion. It was rectangular, thin, and bore a geometric pattern in the particular shades of pink and turquoise so typical of the 1990s. After consulting the family photo albums, we learn I would have been not much older than three around that time.

The inability of adults to remember the first three years of their life is called *infantile amnesia*, and research shows that this experience is common to most people. Try it out for yourself, what is the oldest memory you can recall? Less common and more profound forms of amnesia such as the famous case of patient HM (Scoville & Milner, 1957) have captured the attention of neuroscientists and shone a light on the hippocampus as the seat of our episodic memory, i.e., memory for life events. However, it was the Nobel prize in Physiology or Medicine awarded in 2014 to John O'Keefe, May-Britt Moser, and Edvard Moser for their discoveries of place and grid cells that captured my interest in neuroscience. Soon afterwards, I learned that these exact cells might even hold the key to understanding why episodic memory starts to emerge from three years of age, how new experiences become long lasting memories. Yet despite this progress, the most common form of amnesia that we all suffer from remains relatively unexplained.

The reason for this knowledge gap reflects the difficulty associated with recording from the living, developing brain. However, the past decade has seen important advances on this front. As such, enormous opportunities now exist for elucidating the neuronal mechanisms that support the developmental emergence of episodic memory. The main goal of my thesis was to chart the relationship between the development of *episodic(-like) memory* capabilities in rat pups and the maturation of hippocampal functional representations (place cell coding, Chapter 3) and network activity mechanisms (reactivations, Chapter 4). Relatedly, I also sought to bridge human and non-human animal research on episodic memory development. Humane behavioural research carried out over the past decades has highlighted the ontogeny of core processes of episodic memory while rodent and non-human primate research has started to give insight into the key neuronal substrates of episodic memory development. However, interactions between psychologists and neuroscientists have remained limited which has hindered the impact of seminal research findings. Thus, in order to start building bridges between the fields I carried out a comparative review of episodic memory development research in different mammalian (human, non-human primate, rodent) species (Chapter 2).

1.2 Memory development

Episodic memory is one of the most studied cognitive functions. It is the ability to recall rich detailed experiences, described as "a memory for what happened where and when" (Endel Tulving, 1972). For that reason, it is sometimes referred to as *'what-where-when' (WWW) memory*. The leading theories of memory agree that soon after an experience, the neural trace of memory is predominantly dependent on the cells and circuits in the hippocampus. Over time, the hippocampus makes connections to distal cortical areas, and through repeated reactivation of the same pathways the connections of this distributed cortical code are strengthened. Once the cortical memory trace strengthens sufficiently, it becomes less dependent on the hippocampus for recall. This process is called *systems memory consolidation* (Squire et al., 2015). The initial importance of the hippocampus is demonstrated by clinical case studies of hippocampal damage or experiments that lesion the hippocampus, which leads to anterograde amnesia, i.e., the inability to form new memories (Scoville & Milner, 1957; Spiers et al., 2001; Zola-Morgan & Squire, 1990). However, lesioning the hippocampus at longer intervals after the initial experience yields gradually weaker amnesic effects at recall (Zola-Morgan & Squire, 1990). In other words, hippocampal lesions produce temporally graded retrograde amnesia. The most recent memories that still depend on the hippocampus are vulnerable to hippocampal damage, whereas older memories that have been consolidated may remain relatively unaffected from it. It is almost paradoxical given this theoretical framework that most of our very oldest experiences from infancy and early childhood seem to be permanently inaccessible (Rubin, 2000).

In this section I will briefly summarise findings from the literature describing memory development in humans and rodents. Development of human episodic memory is outlined with regards to the age at which different aspects of WWW memory emerge (Fig 1.1C), and relevant studies are described. Rodent memory development is the focus of experimental work presented in this thesis. A natural point of contention pertains to the question whether rodents truly possess episodic memory. Since rodents are a non-verbal species, I assess the development of their memory capabilities in relation to the individual aspects of WWW framework as insight into the development of episodic-like memory capabilities. Further discussion of memory development in different species is presented in Chapter 2.

1.2.1 Human memory development

One of the hallmarks of human cognitive development is the rapid acquisition of skill, language, and factual knowledge in the first years of life. However, despite being excellent learners, children's memories of events are often inaccurate and unreliable. A wealth of developmental research suggests the first ~two years in human life are characterised by a dense form of amnesia often termed infantile amnesia (Rubin, 2000). From ~2 years of age to at least five years of age, children's ability to recall memories with precision and detail gradually improves. However, their memory capabilities are still limited compared to adults, leading to a phenomenon known as *childhood amnesia* (but see Chapter 2 for a critique of the infantile and childhood amnesia terms). This section will summarize the literature on children's memory abilities during infancy and childhood, highlighting the gradual emergence of different aspects necessary for episodic memory.

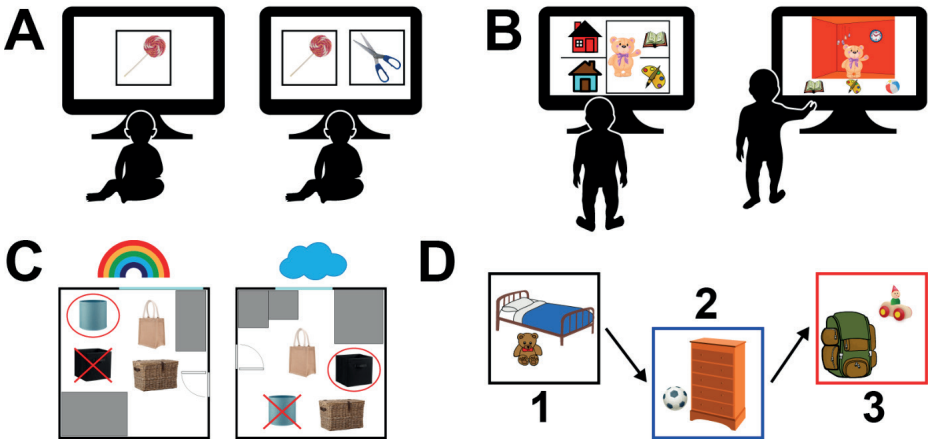


Figure 1.1. Common experimental paradigms used in memory development research. Schematic diagrams of **(A)** visual-paired comparison paradigm used to test item recognition, and **(B)** relational memory task used in (Ngo et al., 2018), **(C)** multiple room-container paired contextual task used in (N. Newcombe et al., 2014), and **(D)** episodic-like memory task in (Harlene Hayne & Kana Imuta, 2011).

Non-verbal paradigms such as visual paired comparisons (VPC), which rely on the infant's tendency to attend to a novel stimulus more than a familiar stimulus (Fig 1.1A), have shown 'what'-memory encoding i.e., the ability to recognise familiar objects presented minutes earlier, to be present already in infancy as early as 36 months of age (Fagan III, 1973; Pascalis et al., 1998b). In early childhood (from ~20months of age) children begin to form simple contextual associations. For example, they can learn the location of a reward hidden in identical containers in two different environments (Fig 1.1C). Thus, the ability to encode 'what-where'

associations, a precursor to WWW memory, begins to emerge around 2 years of age (N. Newcombe et al., 2014). Importantly, studies that tested the accuracy of 'what-where' memory, by adding multiple items of varied similarity (Fig 1.1B), showed that associative memory of this kind continues to develop between 4 and 6 years of age (Ngo et al., 2018). The 'when' component of episodic memory may be the last to emerge, with the earliest emergence being documented around three years of age. As demonstrated by (Harlene Hayne & Kana Imuta, 2011) who hid items ('what') in different locations and rooms ('where') in a specific order ('when') (Fig 1.1D). They found that comparing the performance of children aged 3 and 4 respectively showed no significant difference in remembering what was hidden in which room ('what-where'), but the younger group had difficulties with remembering the order of events taking place during the episode ('what-where-when'). Memory retention follows a similar developmental trend. Simple item ('what') memory can be retained for several weeks by infants as young as 6 months (J. F. Fagan, 1973). Retrieval of contextual memory at short intervals (e.g., 5 minutes up to 24 hours) is possible to some degree around 4 years of age, at the same time that contextual encoding becomes possible (Benear et al., 2021). However, retention of 'what-where' memories over longer periods of time such as a week or longer has been shown to continue emerging into the school years (Bauer et al., 2012; Saragosa-Harris et al., 2021b).

An extensive body of research suggests the hippocampus plays a key role in human memory development. Namely, injury to the hippocampus in early life leads to deficits to episodic memory development causing *developmental amnesia* (DA) (Vargha-Khadem et al., 1997). Remarkably, individuals with DA can attain age-appropriate scholastic achievements and in many aspects develop normally. The symptoms of DA are specific to episodic memory, meaning these individuals can learn facts and skills but never develop the ability to recall lived experiences (Elward & Vargha-Khadem, 2018a). In healthy humans, the hippocampus undergoes extensive morphological development in the first year of life as its subfields double in size (Gilmore et al., 2011; A. Keresztes et al., 2018). It has been shown that the size of the hippocampus in childhood between the ages of 4 and 8 directly relates to memory performance (Riggins et al., 2018). Moreover, fibre tracts that connect the hippocampus to the pre-frontal cortex (PFC) – another brain region implicated in episodic memory (Euston et al., 2012; Simons & Spiers, 2003) - also undergo significant development in early-life. Early-life hippocampal development is therefore causally linked to ontogeny of episodic memory.

1.2.2 Rodent memory development

The particular advantage of rodents as an animal model is the fact that we can not only study the development of episodic(-like) memory capabilities but also the maturation of neurophysiological processes implicated in episodic memory. Rodents are born relatively immature, unable to see, hear, or move independently. Their sensorimotor abilities mature in the second week of life, and by the end of that period they are ready to begin exploring the world outside their nest. Yet, much as in humans, the development episodic(-like) memory is relatively delayed and protracted in rodents. The first signs of episodic(-like) memory begin to emerge towards the end of the third postnatal week (Fig 1.2).

The earliest form of WWW memory to emerge is memory for objects i.e., the 'what' in WWW memory (Ainge & Langston, 2012; Ennaceur & Delacour, 1988). To test this, a pup is placed in an arena containing two identical objects and allowed to investigate the objects. After a short (2min) delay period spent outside the arena, one of the objects is replaced by a novel object and the animal is reintroduced into the arena. Adult rodents intuitively exhibit preference for novelty which can be observed as an increased duration spent investigating the novel object. Therefore, relative maturity of a pup's recognition of a familiar object can be tested, and studies indicate it is mature in the third week post-natal week (Ramsaran, Westbrook, et al., 2016).

Only during the fourth and fifth postnatal week do rodents begin showing signs of the ability to remember the *location* of a familiar object in their environment, satisfying the conditions for 'what-where' memory. A common experimental setup to test spatial memory involves an arena with multiple distinct objects. After a delay spent outside the arena, one of the objects is replaced with an identical copy of the other object (Fig 1.3A). Upon reintroduction, the animal is expected to display associative spatial memory by recognising that one object is in a novel location (Ainge & Langston, 2012). Using two arenas each with their own identical pair of objects can be used to test the contextual aspect of 'what-where' memory (Fig 1.3B). The animal is exposed to both arenas successively, then after a short delay reintroduced into one of the arenas, but with one of its objects replaced with an object from the other arena. Showing novelty response to the object that is familiar to the animal, but specifically novel in the context of that arena displays context-dependent memory. The ability to encode this kind of memory emerges later, in the fourth week of life, and gradually improves through the fifth week of life (Asiminas, Booker, et al., 2022; Ramsaran, Sanders, et al., 2016). Testing the 'when' component of episodic memory is especially challenging in rodents, as this is usually tested

verbally in humans. However, experiments testing a complex combination of object, place, and context recognition has been argued to represent a proxy for WWW (episodic-like) memory. Asiminas, Booker, et al. (2022) exposed animals to two different objects in context A. After a short delay the animals were placed into a different context B containing the same objects as context A but with their locations swapped. Finally, the animals are tested in one of the two contexts with two copies of one of the objects (Fig 1.3C). The animals are required to encode the context as well as the object locations, in order to detect the novel configuration in the tested phase. Their results suggest that the encoding of such episodic-like memory only emerges around 7 weeks of age.

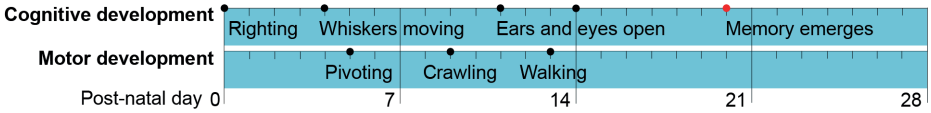


Figure 1.2. Timeline of rodent sensorimotor development and estimated emergence of episodic-like memory.

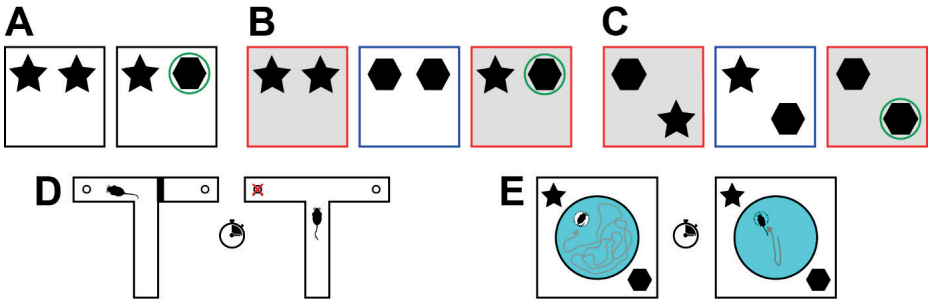


Figure 1.3. Schematic representation of behavioural tasks commonly used to test rodent WWW memory. Different symbols represent distinct objects, green circles represent the object that indicates memory if attended to, red and blue borders represent distinct environments. **(A)** Object-location task, **(B)** Object-in-context recognition task, **(C)** Object-in-location-and-context task, **(D)** Discrete trials delayed alternation T-maze task, **(E)** watermaze.

The emergence of what-where spatial/contextual memory studied using novelty detection paradigms agrees with findings observed on traditional spatial memory tasks performed in mazes. *Watermaze* studies in which animals are tasked to navigate a pool of water to a learned location of a hidden platform (R. G. M. Morris et al., 1982) have played an important role in understanding the spatial memory in rodents. Furthermore, watermaze tasks rely on an external global cues for

orientation (Fig 1.3E). As such, they are a test of allocentric spatial memory, which is thought to be intrinsically linked with episodic memory capabilities (Guderian et al., 2015). The ability to perform watermaze tasks has been observed around 3 weeks of age, rather early in comparison to other studies of contextual memory development (Rudy et al., 1987). However, task design has a considerable impact on these results as early in life pups may not be relying on an allocentric reference frame to carry out the task, but may rather be using proximal or directional cues to solve the task. Akers et al. (2009) showed that rat pups can solve a direction watermaze task at p21, but the ability to solve an allocentric place task emerges only at p26.

Rodent developmental research also commonly tests spatial memory capability using T-mazes (Fig 1.3D). In these tasks animals are either required to learn the location of a reward in the maze (reference memory) or they need to learn to alternate between turning left and right on consecutive trials (Tonkiss et al., 1990). The alternation version of the task is additionally thought to require working memory capability (Dudchenko, 2004). Seminal work has shown that rodents as young as 2-weeks-old can carry out the reference memory version of the T-maze task accurately while the working memory version does not mature until at fourth post-natal week – similar to other forms of 'what-where' memory (Green & Stanton, 1989a). In chapters 3 and 4 I used a version of T-maze alternation to study memory development.

1.3 Neurobiology of episodic memory

In this section, I review the key neuronal substrates and circuit mechanisms implicated in episodic memory, providing the necessary background literature for the findings discussed in Chapters 3 and 4. The discussion will focus on the rodent hippocampus.

1.3.1 Neural substrates and circuits

As outlined in the previous sections, the hippocampus has repeatedly been shown to be central to episodic memory. Damage to the hippocampus specifically leads to severe impairments to episodic memory function (Tulving & Markowitsch, 1998).

The hippocampus (HPC) is a sub-cortical structure located in the medial temporal lobe. It is closely related and connected to a set of neighbouring brain areas sometimes collectively referred to as the hippocampal formation, which include the subiculum, dentate gyrus (DG), and *entorhinal cortex* (EC). The HPC itself is anatomically divided into three *Cornu Ammonis* (CA) subfields referred to as CA1,

CA2, and CA3. Since the experiments and data discussed in Chapters 3 and 4 of this thesis are based on cells recorded from CA1, this area will be the main focus of the current discussion. CA1 is further divided into sub-layers. Stratum lacunosum moleculare (slm) sublayer contains the apical dendrites of the CA1 pyramidal cells and receives direct input from layer three of the EC. Stratum radiatum (sr) mainly receives input from CA3 via the Schaffer Collaterals. Stratum pyramidale (so) contains cell bodies of hippocampal pyramidal neurons and the stratum oriens (so) contains basal dendrites of the pyramidal cells (van Strien et al., 2009).

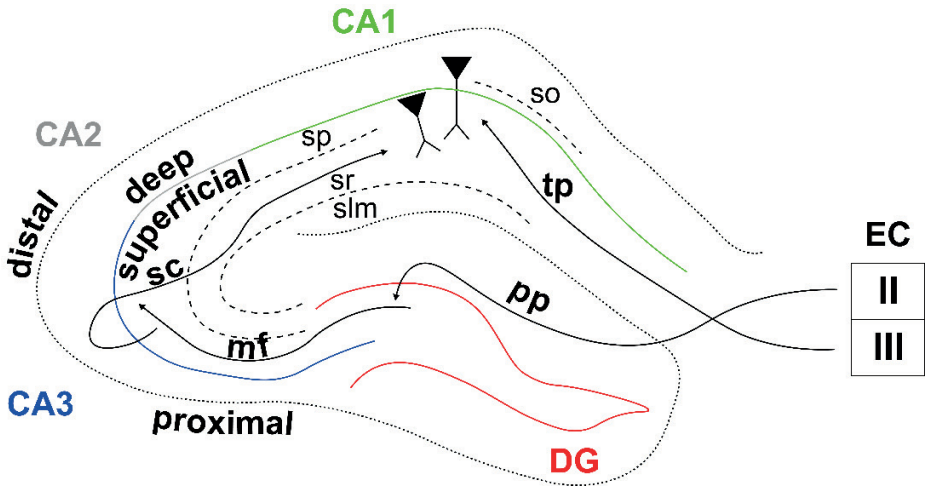


Figure 1.4. Schematic diagram of hippocampal anatomy and principal pathways in the rodent. Subfields CA1-CA3, as well as dentate gyrus (DG) are marked in different colours. Pathways are noted in lowercase abbreviations: temporoammonic pathway (tp), perforant pathway (pp), mossy fibres (mf), Schaffer collaterals (sc). Sublayers are outlined in dashed lines and noted in lowercase abbreviations: stratum oriens (so), stratum pyramidale (sp), stratum radiatum (sr), stratum lacunosum moleculare (slm). EC II and III stand for layers II and III of the entorhinal cortex.

One of the main cortical inputs into the HPC originates in the superficial layers of the EC (Fig 1.4). There are two main pathways from the EC to the hippocampus. One called the indirect pathway begins in the layer II of the EC which connects via the perforant path to granule cells in the DG. From there the information continues via the mossy fibre pathway to neurons in the CA3 subfield of the HPC. Finally, via the CA3 Schaffer collaterals the information reaches the CA1 subfield of the HPC. From CA1, information is transmitted to the deep layers (V/VI) of the entorhinal cortex and the subiculum. The second pathway is called the direct or temporo-ammonic pathway. It describes the inputs that the HPC receives via projections from layer III of the EC directly to the CA1 subfield (van Strien et al., 2009).

Lesioning of the HPC has been shown to cause amnesia (Scoville & Milner, 1957). Even temporary disruption of HPC function, such as electroconvulsive therapy, produces reversible retrograde amnesia whereby remote memories are spared and recent memories forgotten (Squire et al., 1975). Importantly, working and skill-based memory are often somewhat spared in patients with medial temporal lobe (including HPC) damage (Drachman & Arbit, 1966), as are semantic (i.e., memory for facts abstracted of individual experience, (Endel Tulving, 1972)) and recognition memory (Adlam et al., 2009; Baddeley et al., 2001). These findings have been replicated in non-human primates (Squire & Zola-Morgan, 1991) and rodents (Sutherland et al., 2010). Episodic memory function is also thought to depend on HPC - prefrontal cortex (PFC) communication (Simons & Spiers, 2003). Lesioning of PFC or PFC-HPC connections impairs memory retrieval (Floresco et al., 1997), spatial working memory and goal-directed behaviour (Wang & Cai, 2006), as well as episodic-like memory tasks which test all three elements of WWW memory (Chao et al., 2016).

1.3.2 Neural mechanisms supporting episodic memory

A defining feature of the principal neurons of the hippocampal formation is that they carry information about an animals' spatial location and/or orientation in space. Head direction (HD) cells, found in the Subiculum, EC, thalamus and retrosplenial cortex, encode a preferred direction the animal is facing regardless of its location in the environment (Taube et al., 1990). Grid cells, predominantly found in the EC, respond in a regular hexagonal pattern of firing fields that tessellates explored environments (Hafting et al., 2005). Border cells, found in the Subiculum and EC, encode environmental boundaries and/or drop-edges (Barry et al., 2006; Solstad et al., 2008). Integration of the information carried by these different cells is likely involved in the formation of hippocampal place cells which are thought to provide a the *cognitive map* of the environment (Nadel & O'Keefe, 1978). Place cells are the main cell type of interest for this thesis and I describe their function in more detail below.

Place cells. O'Keefe and Dostrovsky (1971) recorded extracellular potentials of single cells in the hippocampus and discovered the still pre-eminent cellular model of memory – the place cell. Place cells are pyramidal neurons found in areas CA1, CA2, and CA3. The main characteristic of place cell activity is the strong spatial modulation observed in their activity, such that a given place cells tends to predominantly fire when an animal is located in a confined region of an environment – its *place field* (O'Keefe, 1976). A standard setup for studying place cells involves implanting electrodes (such as tetrodes or silicon probes) in the pyramidal layer

of the CA1, and letting the animal explore an arena (Fig 1.5A). By concurrently recording action potentials of multiple individual neurons and correlating them to the animal's location in the arena, it becomes apparent that spikes of individual cells tend to cluster in individual locations. Each individual place cell usually has one place field per environment and different place cells prefer to fire in different locations in different? environment. Thus, by recording from a population of place cells, an animal's spatial location can be decoded with high accuracy (Wilson & McNaughton, 1993).

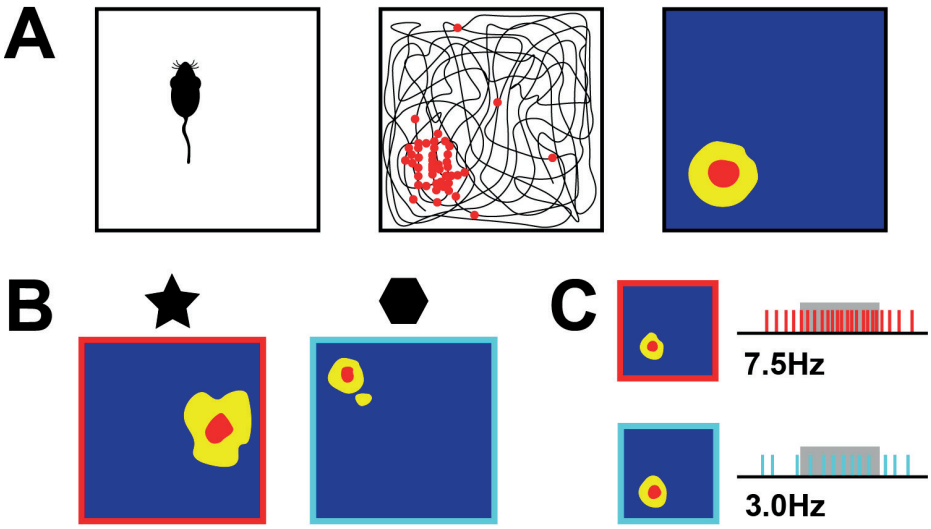


Figure 1.5. Schematic diagram of a representative place cell. (A) Left panel: rodent in an experimental box; middle panel: animal's path traced in black line, single CA1 pyramidal cell action potentials overlaid in red dots; right panel: ratemap of the spike data shown in the middle, hotter colours indicate more spiking (i.e., the location of the place cell's place field). **(B)** Schematic diagram of global remapping. Red and cyan borders represent two distinct environments, the two symbols above the environments represent distal cues (i.e., landmarks). **(C)** Schematic diagram of rate remapping. Red and cyan borders represent different wall colours (i.e., contextual cues), the corresponding vertical bars represent spikes of the depicted place cell as the animal crosses its place field (grey zone). Numbers represent average peak firing rate represented on each plot.

The location in which a place cell fires bears no relation to where it fires, or whether it fires at all, in a different environment - a phenomenon known as (global) remapping (Fig 1.5B). Furthermore, a large body of research has demonstrated that remapping can be elicited by a variety of factors. Muller and Kubie (1987) recorded place cells from rats in a cylindrical environment with a white cue card on the wall. They observed that rotating the location of the cue around the environment resulted in a rotation in place fields such that the fields remained constant relative to the cue

card. Changing the size and shape of the cue card produced no change in the place fields. However, removing the cue caused the place cells to fire in unpredictable locations. Changing the size of the environment itself caused half of the place cells to change their place field unpredictably, and the rest to retain relative position but scale in size. The effect of changing the size and shape of the environment has been modelled by O'Keefe and Burgess (1996) who demonstrated that place cells rely on allocentric cues such as distance from environment walls, and a geometric manipulation (e.g. doubling the length of one wall turning a square environment into a rectangular one) will produce a proportional change of the spatial tuning curve (lengthening of place fields located along the affect wall). Finally, Muller and Kubie (1987) showed that changing the geometric shape entirely (from a cylinder to a rectangular arena) led place cell firing to become entirely unrelated to the activity in the cylindrical environment. When place fields change location in response to changes in the environment, this creates completely orthogonal neural representations of different environments, which is called *global remapping*. Some other sensory changes to the environment that have been shown to induce global remapping are a change of landmark (Bostock et al., 1991), wall colour (Hayman et al., 2003), or moving the recording enclosure to a different experimental room (Fyhn et al., 2007). Place cells can encode complex combinations of multiple contextual cues as demonstrated by Anderson and Jeffery (2003) who recorded place cells in four different pairings of two distinct odours and wall colours, and found that most cells remapped to complex combinations of both odours and wall colours.

However, some changes to the environment do not elicit global remapping, but rather lead to a more subtle form of remapping known as *rate (i.e. partial) remapping* (Fig 1.5C). It was initially described in a study by Wood et al. (1999) who taught rats to dig for a hidden food reward in response to smell, and not location. This allowed them to observe place cell responses to rewarded and unrewarded stimuli in the same location, and demonstrate that place cells can encode the information of different task-related odours by adjusting their mean firing rate without changing the location of their place field. Leutgeb et al. (2005) found that changing that changing the visual cue within the same environment induced rate remapping, whilst moving the animal between different environments with identical visual cues indued global remapping, which led them to propose that these might be two mechanisms serving complementary purposes for episodic memory. Global remapping determines the general location and reflects big changes in the environment, whereas rate remapping instead reflects smaller sensory changes in order to distinguish between similar events within in the same environment.

Place cell remapping is also influenced by the animal's behavioural state or task demands. Markus et al. (1995) compared place cell activity of rats randomly foraging in an open field to that of rats foraging between multiple learned reward locations in the same environment, and demonstrated that place cells can remap to represent different task demands. Place cells were first observed during random foraging, then subsequently animals were tasked to search between stable reward locations in the same environment which caused global remapping, however on a subsequent random foraging trial the cells recovered their place fields from the original random foraging trial. Wood et al. (2000) tested whether place cells can distinguish between two different types of trials within a memory task. The task was to continuously alternate between taking left and right turns on a T-maze. Since both left-turn and right-turn trials share the central stem of the T-maze, the authors compared the activity of place cells on the central stem in the two trial types and observed that some place cells fired only in left-turn or right-turn trials, and some fired in both trial types but exhibited trial-type dependent global remapping. Remapping that may reflect which trajectory the animal is on or its intended destination is also known as *splitter cell* remapping. Griffin et al. (2007) had rats perform a T-maze delayed-nonmatch-to-place (DNMP) task in which each trial consists of an encoding and retrieval phase. The animal is initially forced to run into one arm of the T-maze, followed by a 10-20 second delay before reinterring the track with the task to recall which arm it was forced into and choose to visit the opposite arm. By comparing the place cell activity in forced and choice runs, the authors found that most place cells were selectively active in either one of the two trial types. The majority of cells did not preferentially activate for left nor right turns on the track (i.e. displayed splitter cell remapping), indicating that the place cells, in this task, specifically represented the encoding or retrieval phase of the task. Robitsek et al. (2013) further showed that place cell remapping before a choice point in a delayed alternation T-maze task predicted successful memory performance. They compared the activity of place cells on the central stem i.e., the phase of the task when the animal is required to recall the last trial in order to correctly alternate, finding that remapping of >90% of the recorded place cells correlated with correct trials. In Chapter 3, I describe an experiment in which we used the DNMP task to study the ontogeny of hippocampal representations in relation to the development of episodic(-like) memory.

Theta-band oscillations. The dominant oscillation observed in the hippocampal local field potential (LFP) during locomotion is the theta rhythm (Vanderwolf, 1988), in rodents defined as an oscillation in the 6-12Hz range. *Theta-band oscillations* have long been implicated in episodic memory (Landfield et al., 1972; Winson, 1978).

Interneurons from the medial septum that project to the hippocampal formation are thought to be the main theta generator as lesions to the area abolish hippocampal theta (Green & Arduini, 1954). Individual place cells do not require hippocampal theta for place field formation or maintenance (Brandon et al., 2014), however *theta phase precession* provides place cells with an additional phase code (O'Keefe & Recce, 1993; Skaggs et al., 1996). Theta phase precession describes the phenomenon that place cells tend to fire in the late phase of theta as the animal is entering its place field, in the trough of theta when the animal is in the centre of the place field, and at progressively earlier phases of theta as the animal leaves the place field (Fig 1.6). Recent data indicate that phase precession might reflect the change in balance of CA1 glutamatergic inputs (Guardamagna et al., 2023). The main driver of CA1 place cell activity is CA3 input, which arrives into CA1 near the through of CA1 theta resulting in preferential CA1 spiking near the trough. However, if the EC input becomes a dominant influence on CA1 activity, it biases CA1 activity towards earlier phases of theta, thereby producing the phase shift associated with phase precession.

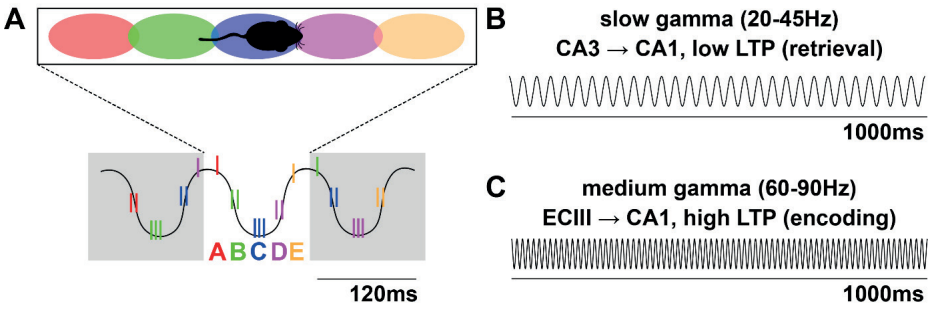


Figure 1.6. Schematic diagrams of hippocampal oscillations and related mechanisms. **(A)** Theta sequences and phase precession. Different colours depict individual place cells with spatially distinct fields on the track (top panel), and spikes on the underlying hippocampal theta (bottom panel), **(B)** slow gamma implicated in memory retrieval, and **(C)** medium gamma implicated in memory encoding.

Influential models of theta-related firing in CA1suggest that the balance between CA1 inputs controls different memory operations, such as encoding and retrieval. Hasselmo et al. (2002) proposed a model in which the strong EC input coincides with relatively weak CA3 input and increase in long-term potentiation in CA1, thereby facilitating encoding. Conversely, the strongest phase of CA3 input coincides with weak EC input and less long-term potentiation, which prevents disruptive re-encoding and instead promotes retrieval by preferentially reactivating

previously potentiated synapses. Siegle and Wilson (2014) provided experimental evidence for this model by selectively inhibiting CA1 activity at either the peak or through of theta, as mice were performing a spatial non-match to sample task in a H-maze. The animals started each trial in a randomized arm of the H-maze, and the task was to traverse across the central stem and towards the other pair of reward arms and choose the one closer to the starting arm. The time spent in the starting arm was considered the encoding phase, and the time spent on the central stem was considered the retrieval phase. The authors observed that optogenetic inhibition of CA1 when the CA3 inputs should dominate, improved performance when stimulated in the encoding section of the track and not when stimulated in the retrieval section. The results were the opposite for CA1 inhibition when the EC inputs should dominate, which enhanced performance when stimulated in retrieval sections, but not in encoding sections. The fact that CA1 inhibition improved performance indicates that task-irrelevant inputs (i.e., EC for retrieval and CA3 for encoding) may have been selectively silenced, confirming the different roles of theta phases based on their dominant inputs.

Although the exact function of phase precession is still debated, one view states phase precession gives rise to so-called *theta sequences* – place cell ensembles tying together space behind and ahead of the animal in a regular pattern within a single theta cycle (Dragoi & Buzsáki, 2006; Foster & Wilson, 2007). Theta sequences are thought to compress multiunit place cell activity into time scales compatible for spike-timing dependent plasticity (Skaggs et al., 1996) and thereby may support memory formation. Wang et al. (2015) trained rats on a spatial delayed alternation task, in which the animals had to alternate between two arms and spent the short delay period between arms in a running wheel so theta sequences could be observed without additional sensory input. They found disrupting theta sequences during the delay period impaired memory performance.

Another major hippocampal rhythm are *gamma oscillations* (~25-100Hz). Studies often differentiate between slow (20-45Hz), medium (60-90Hz), and fast (100-180Hz) gamma (Colgin et al., 2009). Slow and medium gamma bands are thought to be generated by distinct sources with slow gamma arising from the CA3 (Csicsvari et al., 2003), and medium gamma from EC and DG (Colgin et al., 2009; Fernández-Ruiz et al., 2021). The two gamma bands arriving from the two major CA1 inputs also maintain temporal segregation by peaking at different phases of the theta cycle (Schomburg et al., 2014). It has been proposed that the two gamma bands in the HPC might support distinct memory functions (Bieri et al., 2014). Slow CA3-CA1 gamma might be too slow for optimal inter-spike interval for synaptic plasticity

(>25ms) (Bi & Poo, 1998), which allows it to activate specific cell assemblies involved in retrieval of previously encoded memory, whilst preventing re-encoding of the memory trace (Colgin & Moser, 2010). Montgomery and Buzsáki (2007) recorded hippocampal oscillations from rats learning a delayed spatial alternation task and observed retrieval-related increase in CA1 slow gamma power as well as gamma coherence between CA3 and CA1. These increases were specific to the central stem of the maze, the location in which the animal is required to recall the information from the previous trial in order to make a correct choice. Medium gamma spike timing has been shown to optimise conditions for long-term potentiation, and is closely related to the EC input into CA1 making it a strong candidate mechanism for integration of cortical sensory information into the HPC (Zheng et al., 2016).

Sharp-wave ripples. During periods of quiescence, and especially during NREM sleep, a complex compound LFP signal called a *sharp-wave ripple* (SWR) can be observed in the hippocampal CA1 subfield (Buzsáki, 2015). SWRs are aperiodic oscillations reflecting highly coordinated CA1 population activity lasting ~50-100ms. The sharp wave component reflects coordinated discharge of excitatory neurons from CA3 which leads to sharp depolarisation in the CA1 apical dendrites. There is extensive evidence that this strong synchronised bursting of CA3 is intrinsic to its circuitry (Suzuki & Smith, 1988), and that it might even be the default mode of the CA3 when not supressed by subcortical neuromodulators such as cholinergic neurons from the medial septum (Vandecasteele et al., 2014). The CA3 output activates CA1 interneurons which engages a cascade of excitation and inhibition between pyramidal cells and interneurons in CA1 giving rise to the high-frequency (125-250Hz) ripple component (Buzsáki et al., 1992).

Sleep is thought to support memory (Rasch & Born, 2013), and as a prominent hippocampal NREM sleep signature, SWRs have long been implicated in systems memory consolidation (Buzsáki, 2015). SWR occurrence is closely coordinated with the occurrence of other sleep-related oscillations implicated in learning. SWRs peak before the neocortical peak of spindle activity - a cortical correlate of memory consolidation (Clemens et al., 2007; Lüthi, 2014; Siapas & Wilson, 1998). Furthermore, SWRs have been causally linked to memory consolidation in rodents. Girardeau et al. (2009) conducted a closed loop experiment in which they detected an incoming SWR and disrupted the coordinated firing of local CA1 circuitry thereby preventing the occurrence of SWRs, and observed impaired learning on a memory task. Maingret et al. (2016) let rats explore two objects for either 3 or 20 minutes, and tested recall by changing the location of one of the objects on the following day. 20-minute exposure was accompanied by increased coupling of SWRs to

cortical spindles and delta waves and led to successful recall on the following day, indicating some degree of consolidation. Whereas 3-minute exposure did not result in increased HPC-PFC coupling and produced chance performance on the following day. However, the authors were able to induce consolidation after 3-minute exposure by stimulating the PFC upon detection of SWRs, which produced significant recall on the following day. This finding confirmed that SWRs directly coordinate activity with cortical areas in a way proposed by the theory of systems memory consolidation.

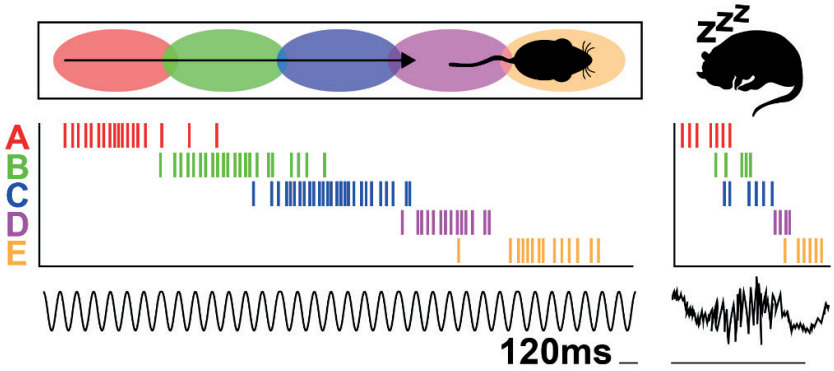


Figure 1.7. Schematic representation of hippocampal replay. Left raster plot: spikes of individually coloured place cells (A-E) activating in a sequence as an animal traverses the track, with movement-related theta rhythm underneath. Right raster plot: during subsequent sleep, the same sequence of cells activate in the same order within the sharp-wave ripples depicted underneath.

However, SRWs have also been shown to support spatial and WM. Disruption of awake SWRs also disrupts WM in a spatial alternation task (Jadhav et al., 2012). Ego-Stengel and Wilson (2010) had rats navigate two identical mazes to collect a food reward, but disrupted SWR activity in post-run sleep after the session in only one of the two mazes. They observed that animals took longer to locate the reward in the maze with disrupted SWRs, than in the maze with uninterrupted SWRs. Duration of SWRs has been shown to positively correlate with learning to associate odours to reward locations (Eschenko et al., 2008), and spatial working memory in a radial arm maze (Ramadan et al., 2009). Memory performance can be predicted by increased occurrence of awake SWRs at reward locations in a spatial learning task (Dupret et al., 2010). The causal link between the duration of SWRs and learning has recently been established by Fernández-Ruiz et al. (2019) who used optogenetics to artificially prolong SWRs and observed an improvement in learning. We charted the maturation of SWRs in relation to the early post-natal emergence of spatial working memory in a discrete trials T-maze task (Chapter 4).

One of the mechanisms by which SWRs might support memory consolidation is by re-activating wakeful activity patterns. Place cells whose activity is correlated during wakefulness (i.e., overlapping place fields), also display correlated activity during SWRs (Pavlides & Winson, 1989; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). Moreover, place cell sequences reflecting paths an animal travelled during wakefulness can reactivate in exactly the same order as they were experienced in, a phenomenon known as *hippocampal replay* (Lee & Wilson, 2002). As SWRs occur on the ~100 millisecond timescale, replayed experiences are dramatically time compressed, occurring ~10 times faster than during behaviour (Nádasdy et al., 1999; Pfeiffer & Foster, 2015). Reactivations are thought to support memory consolidation via Hebbian learning (Wilson & McNaughton, 1994). Importantly, reactivations and replay require experience and do not simply reflect underlying network connectivity patterns but tend to represent novel and recent experience (Cheng & Frank, 2008; Foster & Wilson, 2006a), as well as preferentially reinstate behaviourally relevant information such as paths to rewarded goals (Singer & Frank, 2009). In a recent study, Gridchyn et al. (2020) trained rats to recognise two different environments, each with its own food reward location. The authors identified neuronal ensembles specific to each environment, and could therefore selectively optogenetically inhibit pyramidal cells related to either environment during sleep, preventing their replay. They found that inhibiting replay of cells coding for one environment during sleep disrupted learning, as the subsequent performance in that environment decreased compared to a control environment which was replayed without interruption. This finding causally implicates the content of hippocampal replay in memory consolidation.

Hippocampal replay does not only occur during sleep, but has also been observed during wakeful periods such as when the animal stops to groom, consume food or make a decision. Awake replay has been proposed to support planning. It occurs more frequently after animals make a correct choice in a spatial alternation task, than when they make a mistake (Singer & Frank, 2009). Diba and Buzsáki (2007) observed that replay trajectories which occurred when the animal came to a stop tended to recapitulate paths in reverse, whereas replay trajectories observed prior to movement initiation tend to reactivate the paths forward. Analogous to the hypothesis that replay of the recently visited paths representing recapitulation, replay of future paths was seen as potential neural mechanism of future planning. Further, Singer et al. (2013a) could accurately predict trial outcomes based on awake replay activity in a spatial alternation task. Similarly, Pfeiffer and Foster (2013b) found that replay trajectories have a tendency to propagate in the direction that the animal subsequently travels in, and this effect was only observed when navigating towards

a learned goal location in an open field and not when foraging randomly, as would be expected if replay supports planning.

Together, these results lend support to the hypothesis that awake replay support future planning, yet a causal link between awake replay and planning has yet to be established and a point of some contention in the field. A number of studies have failed to clearly relate awake replay to immediately relevant behaviour, and instead observed reactivation of remote paths unrelated to the animal's current position and following movement trajectory (Davidson et al., 2009; Gupta et al., 2010; Jackson et al., 2006; Karlsson & Frank, 2009b; Ólafsdóttir et al., 2018; Ólafsdóttir et al., 2017). An alternative approach to assessing whether awake and sleep replay serve different roles might be to study their ontogenetic emergence in order to determine whether their developmental trajectories differ (Chapter 4).

1.4 Rodent hippocampus development

In the last decade, electrophysiological and functional brain imaging methods have been adapted so they can be used to study the developing rodent brain. In this section, I summarise the literature charting the ontogeny and development of functional neuronal mechanisms (outlined in 1.3.2.) implicated in mature episodic (-like) memory.

Spatial cells. The earliest spatial cells of the hippocampal formation to mature are HD cells (Langston et al., 2010b; Wills et al., 2010). The first signs of HD cell activity have been observed at P12, before animal's eyes are even open (Bjerknes et al., 2015; Tan et al., 2015). Remarkably, their maturation is rapid and by P15 HD cells are found in larger numbers and their firing becomes adult-like (Tan et al., 2017). This early maturation matches the age that pups begin spontaneously exploring outside their nest (Ruppert et al., 1985). Place cells can be observed at P16, though their firing properties at this age are not adult-like; they display less spatially confined activity and place fields are less stable (Langston et al., 2010b; Wills et al., 2010). Unlike other spatial cells, the developmental trajectory of place cells is gradual and protracted as at time of emergence only a small proportion have adult-like firing properties, and the rest continue to mature with a noticeable increase in spatial coherence, information, and firing rate until at least P45 (Scott et al., 2011). Border cells in the subiculum are present from p16 and continue increasing in number, spatial information, and stability across the following weeks. However, even by the end of the fourth week of life until they still do not reach the firing characteristics observed in adult rats (Muessig et al., 2024). The latest spatial cell of the hippocampal formation to emerge are grid cells, the

first signs of which can be observed at the end of the third week of life, with stable and adult-like activity abruptly emerging shortly thereafter around P20-21 (Wills et al., 2012; Wills et al., 2010). However, data from Langston et al. (2010b) indicate that grid cells do undergo significant improvements in stability and periodicity following their emergence. But by the end of the fourth week of age grid cell firing properties are adult-like.

The early emergence of HD cells indicates their early ontogeny might be due to their independence from inputs of other spatial cells and the HPC itself (Blair et al., 1998). The presence of adult-like preferred firing direction coherence, which is an intrinsic property of the HD cell network (Peyrache et al., 2015), has been observed in pups even before eye opening (Bjerknes et al., 2015). It has been suggested that the emergence of HD cell network marks the start of spatial memory development since these cells do not rely on sensory nor HPC input for their function (Cheung, 2014; Tan et al., 2017). Grid cells on the other hand require input from the HPC in order to maintain their spatial code (Bonnevie et al., 2013). In addition, when the HD cells are silenced in adult rats, grid cells lose their periodicity (Winter et al., 2015), making it likely that the emergence of grid cells requires prior emergence of HD cells and place cells. Interestingly, although place cells emerge earlier than grid cells, abrupt stabilisation of grid cells coincides with the age at which place cells have been observed to greatly improve their spatial accuracy (Muessig et al., 2015). Place cells in adult rats do not require input from grid cells, but do rely on it for accuracy since when inputs from the EC into CA1 are lesioned, the coherence of place cell spatial code is greatly reduced as shown by larger and more disperse firing fields (Brun et al., 2008; Bush et al., 2014; Hales et al., 2014). These results might indicate that although place cells may form without grid cell input, grid cells may nonetheless provide place cells with information that greatly improves the place cell code.

Little is known about the development of different forms of place cell remapping. Muessig et al. (2016) observed evidence of global remapping at P16. Exposure to an exact geometrical replica of the environment, but with olfactory input accumulated from previous exposures removed also induced global remapping, showing the influence of non-spatial variables on place cell remapping.

Theta-band oscillations and sequence coding. Hippocampal oscillations shown to be critical for mature memory function emerge prior to any spatial cell in the hippocampal formation. Gamma oscillations have been observed in rodents as early as P2, but sharply increase in power around P8 when theta oscillations emerge (Leblanc & Bland, 1979; Mohns & Blumberg, 2008). Hippocampal theta rhythm

undergoes a change in amplitude and frequency during the third week of life, on average increasing from 5Hz at P16 to 7Hz at P22, at which point it resembles that observed in adult animals (Wills et al., 2010). The proportion of CA1 cells modulated by the theta frequency also increases significantly and matures to adult-like levels in the same period (Wills et al., 2010). Theta sequences emerge slowly between P17 and P32, gradually depicting longer trajectories behind and ahead of the animal, and become adult-like in the fifth week of life (Muessig et al 2019).

SWR and replay. SWRs undergo protracted development in early life. The sharp wave component of a SWR can be detected in the first postnatal week (Leinekugel, Khazipov, Cannon, Hirase, Ben-Ari, & Buzsáki, 2002). However, the higher frequency components can only be reliably observed after P10 and their emergence has been linked to maturation of inhibition in CA1 that is necessary for their entrainment (Pochinok et al., 2023). Early post-natal SWRs only begin resembling adult SWR activity in terms of power and frequency in the third week of life (Buhl & Buzsáki, 2005). SWRs further continue increasing in power through the 4th week of life at which point they reach adult levels (Farooq & Dragoi, 2019) Due to the relatively early emergence of SWRs, and their intrinsic role in coordinating activity in the hippocampal formation (see 1.3.2), it has been proposed that they might prepare the networks for the subsequent emergence of spatial cells required for episodic memory (Ben-Ari, 2001; Mohns & Blumberg, 2008; Tan et al., 2017). Since spatial cells of the hippocampal formation also begin to functionally emerge in the third week of life, most of the cells involved in hippocampal reactivations and replay are functionally mature at that point in development.

In a recent study, Muessig et al. (2019b) investigated hippocampal replay in rat pups aged P17-P32 as the animals were resting after running on a linear track. Replay sequences were detected at all ages; however, the authors differentiate between early replay events (3rd postnatal week) which only span short portions of the track around a single location (<50cm), and replay sequences at later ages which replay the majority of the track as is expected of mature hippocampal replay. In addition to that, distance replayed correlated strongly with the maturity of theta sequences, indicating that place cell binding via theta sequences might be a necessary precondition for maturation of hippocampal replay. The two mechanisms have previously been functionally linked in adult animals (Drieu et al., 2018). Farooq and Dragoi (2019) also investigated hippocampal replay in rat pups, including rest before and after running on a linear track. Their results suggest that development of the hippocampal network occurs in stages. Between P15-P17 the HPC develops the ability to represent separate locations, without the ability to bind them together.

As pups begin independently leaving the nest between P18-P22, sequential activity beings to emerge and represent recent experience. Then finally in the fourth week of life the system is capable of experience-dependent representations of entire episodes by binding locations through theta sequences which enables their reinstatement in sleep. Replay is therefore the latest mechanism related to memory consolidation that emerges in early post-natal life, and as such might be the final pre-condition for the emergence of episodic memory.

1.5 Thesis statement and outline

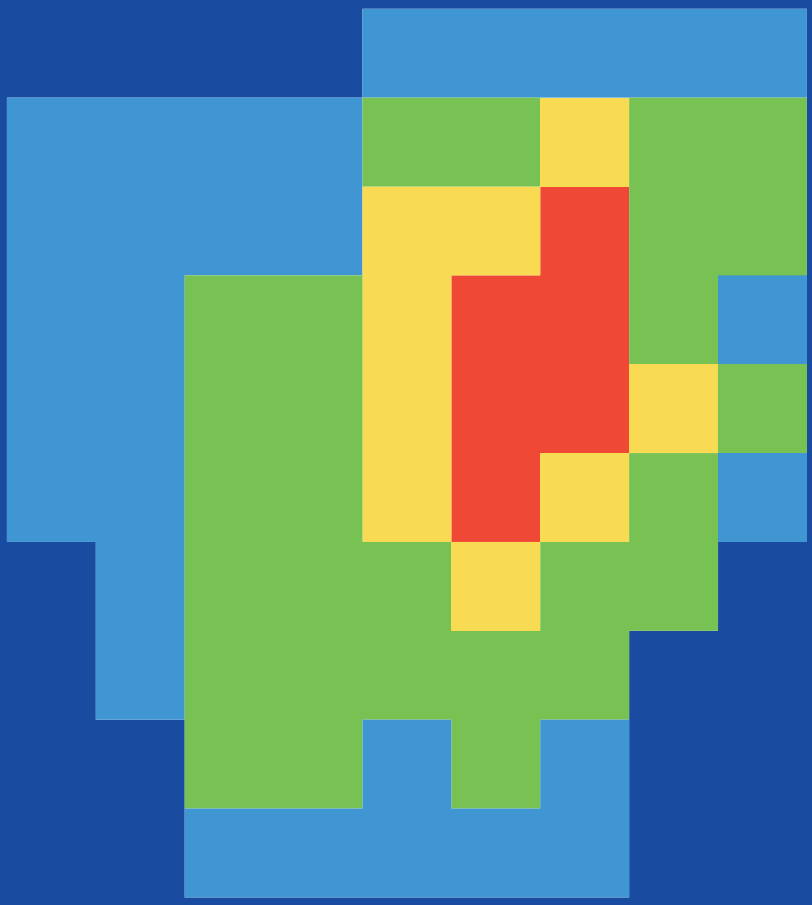
In the preceding sections I have demonstrated that episodic memory in humans and rodents has a comparable, delayed and a protracted developmental trajectory. In **Chapter 2**, we offer a comprehensive review of memory development research by synthesising seminal results across human and non-human animal research to develop a cross-species model of episodic memory development. Critical knowledge gaps and caveats in existing research are highlighted, ultimately deriving prospective advice that should yield a more coherent understanding of memory development. Hippocampal development has been identified as the crucial component in the ontogeny of episodic memory. Namely, the emergence of functional characteristics of spatially modulated cells of the hippocampal network, in particular place cells, and their population mechanisms such as hippocampal replay coincides well the age when episodic-like memory capabilities start to emerge in rodents. However, many knowledge gaps still remain in our understanding of how functional representations and reactivations relate to the protracted emergence of episodic-like memory. Most importantly, no study to date has directly linked behavioural/cognitive and neural development.

To address some of these open questions, for the first time we chronically recorded CA1 single unit activity and LFP from freely moving rat pups as they performed a spatial working memory task. In **Chapter 3**, I describe the experimental design and setup in detail. With our approach, we could model individual animals' developmental trajectories which was essential to relating neuronal development to memory emergence. In this study, we found the development of place cell encoding specificity occurred in parallel with the maturation of spatial working memory. Furthermore, we identified the maturation of the ability of the CA1 network to dynamically switch the balance of CA1 inputs in different task phases as a potential driver of encoding specificity development.

In **Chapter 4**, we investigated the relation of hippocampal population mechanisms implicated in memory consolidation (SWRs, reactivations) and maintenance to the

emergence of working memory. We demonstrated that a developmental increase in sleep sharp-wave ripple duration predicts memory emergence. Concurrently, hippocampal reactivations increased the number of locations depicted without increasing the extent of the track reactivated, indicating that a denser and more detailed representation of the environment might subserve memory emergence. Importantly, by showing that reactivations nearly cease during trials after memory emergence, and increasingly occur after trials, our data suggests that hippocampal replay does not serve the function of immediate planning as previously proposed in the literature.

Our data directly relating neural development to cognitive development is the first of its kind and expands upon the existing literature. In **Chapter 5**, I synthesise the results of Chapters 2-4 and discuss theoretical implications of our results, challenges and caveats, as well as their relation to the current state of the field.



Chapter 2

Episodic memory development: Bridging animal and human research

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Summary

Objective

Human episodic memory is not functionally evident until about 2 years of age and continues to develop into the school years. Behavioural studies have elucidated this developmental timeline and its constituent processes. In tandem, lesion and neurophysiological studies in non-human primates and rodents have identified key neural substrates and circuit mechanisms that may underlie episodic memory development. Despite this progress, collaborative efforts between psychologists and neuroscientists remain limited, hindering progress. Here, we seek to bridge human and non-human episodic memory development research by offering a comparative review of studies using humans, non-human primates, and rodents. We highlight critical theoretical and methodological issues that limit cross-fertilization and propose a common research framework, adaptable to different species, that may facilitate cross-species research endeavours.

Approach

We conducted an extensive cross-species literature review using the framework of "what-where-when" memory as a means to synthesise knowledge of episodic memory development across the literature.

Significance

This review offered a novel comparative analysis of the field, highlighting caveats and knowledge gaps, and providing important considerations to guide future collaborative research.

2.1 Introduction

"Episodic memory" is the ability to anchor memories for events in our lives to their spatiotemporal context and the ability to recall these at later times (Tulving, 1983) ('what-where-when' (W-W-W) memory (E. Tulving, 1972). It is central to our sense of personal identity and supports adaptive everyday decision making and planning. Although the developing infant is a prodigious learner, able to rapidly assimilate world knowledge and acquire language proficiently, the ability to encode and recall detailed episodic memories develops relatively late (Newcombe et al., 2007; Perner & Ruffman, 1995). Specifically, we cannot recall episodic memories from the first ~2years of life (Newcombe et al., 1998; Ribordy et al., 2013; Rubin, 2000), although the ability to encode simple items develops early in infancy, along with the ability to learn facts about the world (Barr et al., 1996; Bauer & Dow, 1994; Newcombe et al., 2007; Vargha-Khadem et al., 1997). By ~2years of age children can form elemental W-W-W memories (Newcombe et al., 1998; Ribordy et al., 2013; Rubin, 2000) - such as knowing the spatial location of a reward (Newcombe et al., 1998; Ribordy et al., 2013). The ability to encode detailed W-W-W memories - where multiple items need to be bound to their spatial-temporal context - and to retain these over extended periods of time, continues to mature until the school years and beyond (Ngo et al., 2018; Perner & Ruffman, 1995; Picard et al., 2009; Ribordy Lambert et al., 2017; Saragosa-Harris et al., 2021a). The late development of episodic memory has often been termed infantile or child amnesia (Freud, 1914). However, we refrain from using these terms as they carry a clinical connotation, which is odd in the context of healthy cognitive development.

Lesion and stereological studies carried out on non-human primates (NHPs) and rodents have highlighted that the protracted development of episodic memory likely depends on the hippocampus (Bachevalier & Vargha-Khadem, 2005; Freeman & Stanton, 1991; Lavenex & Banta Lavenex, 2013), a brain structure important for such memory in adults (Scoville & Milner, 1957). Selective lesions of the hippocampus in developing monkeys, for example, has been found to prevent the maturation of W-W-W memory (Bachevalier, 2019; Zeamer et al., 2015). Further, in recent years, significant advances have been made to our understanding of the neurophysiological basis of episodic memory ontogeny, as neural recording and perturbation tools have started to be applied to the living, developing rodent brain. This research has, for example, elucidated the ontogeny of functional neuronal representations (Langston et al., 2010b; A. I. Ramsaran et al., 2023; Wills et al., 2010), network mechanisms (Farooq & Dragoi, 2019; Muessig et al., 2019a) and oscillations (Buhl & Buzsaki, 2005) thought to contribute to mature episodic memory. Thus, the field is at a critical stage where we are starting to gain unprecedented insight into the cognitive-neurobiological building blocks of episodic memory development.

Despite this progress, comparative efforts between neuroscientists and psychologists have remained limited. Carefully designed tasks set up to measure specific facets of episodic memory in developing children are rarely used in non-human animal studies, and some tasks are not translatable across species. In addition, debates remain regarding whether W-W-W memory truly captures episodic memory, in part because the term has undergone some revision since its first description. Tulving (E Tulving, 1985; Tulving, 2002) proposed that in addition to being a W-W-W memory, a "true" episodic memory is also retrieved via conscious recall ('autonoesis'). However, as autonoetic recall can only be assessed through language, including this criterion has presented significant challenges for studying the cognitive and physiological basis of episodic memory ontogenesis in non-human animals that lack language, and even in children with limited verbal abilities.

Our aim here is to bridge the complementary work of researchers investigating different mammalian species by offering a comparative review through the lens of the W-W-W memory theoretical framework. Specifically, we will review research carried out in humans, non-human primates (NHPs) and rodents to describe key cognitive and neurobiological developmental milestones of W-W-W memory. We will highlight theoretical and methodological caveats that currently limit cross-species translational impact and identify critical knowledge gaps that remain. Although W-W-W memory may be a mere proxy for human episodic memory capability – sometimes termed episodic-like memory (Griffiths et al., 1999) - we believe it represents a valuable tool for studying the ontogeny of this core cognitive capability in comparative research settings.

We structure the review around specific facets of W-W-W memory (e.g. object ('what'), spatial ('what-where'), spatial-temporal ('what-where-when') memory) and discuss the development of encoding and retention/retrieval separately. We will use the terms W-W-W and episodic-like memory interchangeably to refer to memory that fulfils Tulving's original definition of 'what-where-when' episodic memory (E. Tulving, 1972) but where autonoesis cannot be ascertained. Our treatment builds on prior reviews (e.g. (Alberini & Travaglia, 2017; R. Cossart & R. Khazipov, 2022; Donato et al., 2021; Donato et al., 2023; Josselyn & Frankland, 2012; A. Keresztes et al., 2018)), by drawing links between species from two different mammalian groups, discussing cross-species findings explicitly side-by-side and reviewing the literature for different components of W-W-W memory individually. Adopting this methodical and comparative approach offers novel insight into the ontogeny of episodic(-like) memory and may stimulate greater cross-fertilization and the establishment of comparative research partnerships.

2.2 Development of episodic-like encoding

We begin by summarising research on the development of episodic-like memory encoding, i.e., studies where memory testing occurs shortly (<~2-10min) after stimuli sampling.

2.2.1 The development of object ('what') encoding

A key building block for W-W-W associative memory is the ability to encode an object's identity, i.e. the 'what' in W-W-W memory. A wealth of studies, carried out in various mammalian species, have shown that the ability for 'what' encoding matures first. To study object encoding, developmental researchers often rely on the visual paired comparison (VPC) task. The VPC task taps into a developing organism's natural tendency to look more at novel visual stimuli over familiar stimuli (Figure 2.1A). VPC studies have made an important contribution to memory development research, as they can be carried out in pre-verbal infants (as well as older children and even adults with some adaptation) and are amenable to cross-species testing. In humans, novelty preferences on the VPC task have been documented in infants and even neonates (J. F. Fagan, 3rd, 1973; Pascalis et al., 1998a; Pascalis & de Schonen, 1994).

Similarly, in NHPs 'what' encoding has been found to develop in the early post-natal period. By 1.5months mature object encoding has been observed (Bachevalier, 2018). When comparing NHP age to human age, one NHP month is thought to approximate four months in human life, until 2years of age at least (Fortman et al., 2001). Thus, the developmental trajectory of 'what' encoding is comparable in humans and NHPs.

To study the development of object encoding in rodents, researchers typically rely on object recognition (OR) tasks. In OR tasks, rodents explore an environmental arena containing two identical objects. After a short delay, the rodent is placed back into the same arena which now contains one of the original objects and one novel object (Figure 2.1B). If rodents have encoded the object successfully, they should preferentially explore the novel object over the familiar object. Studies have shown that mature OR encoding can be observed reliably from post-natal day 14 (P14) (Cruz-Sanchez et al., 2021; Kruger et al., 2012; Reincke & Hanganu-Opatz, 2017). See Figure 2.1C for a summary developmental timeline of 'what' encoding). Comparing rodent age - counted in days or weeks - to human age is difficult. A 1-week-old rodent is often considered the rough equivalent of a newborn human, on the basis of brain oscillatory patterns (Chini & Hanganu-Opatz, 2021; R. Cossart & R. Khazipov, 2022). In terms of W-W-W memory development, multiple studies suggest the initial inflection points occur ~3 weeks of age (e.g.(Campbell & Spear, 1972; Douglas et al.,

1973b; A. I. Ramsaran et al., 2023; Travaglia et al., 2018). Thus, a 3-week-old rodent may be comparable to a 2-year-old child in terms of memory maturation.

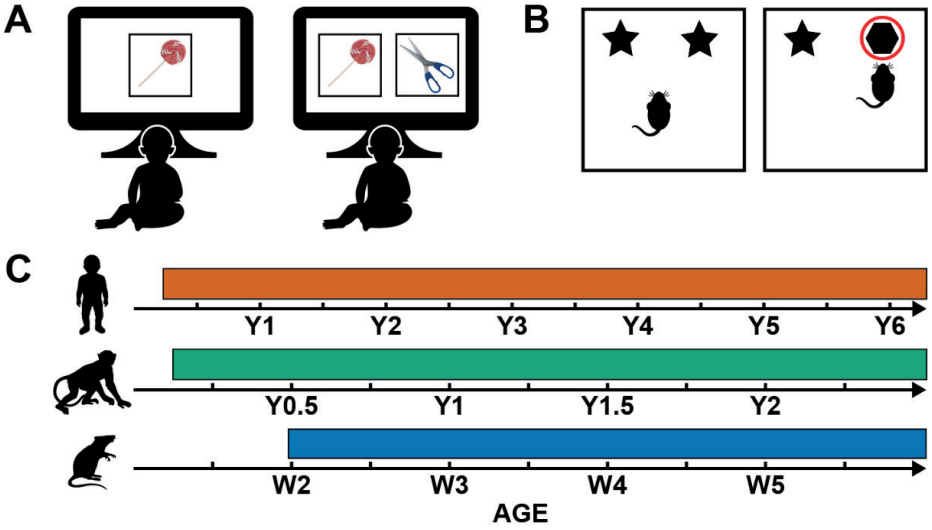

Figure 2.1. Development of 'what' (object) encoding. (A) Schematic diagram of a visual-paired comparison paradigm, and **(B)** object recognition task. **(C)** Developmental timeline of human, non-human primate, and rodent 'what' encoding.

2.2.2 The development of 'what-where' encoding

The ability to associate an object, or multiple objects, to a context and/or a spatial location – i.e. 'what-where' encoding - is a key component of W-W-W memory. The term "context" can refer to the background on which an object is displayed, the environment in which an object is located and/or the specific features of an object's environment. The phrase "spatial position" refers to the allocentric (environment-centric) spatial location of a stimulus within an environment rather than its egocentric location. We review the literature that has charted the ontogeny of these two related forms of 'what-where' encoding.

Contextual 'what-where' encoding

Some studies have found context influences visual preferences on VPC tasks in infants as young as 6 months of age (Haaf et al., 1996), possibly suggesting that contextual 'what-where' encoding may emerge in the neonatal period. Similarly, Rovee-Collier and colleagues (1985) have shown that contextual features (crib bumper designs) influence the ability of infants to display a learned action association (a kick leading to movement in an overhead mobile) (Rovee-Collier et

al., 1985). However, studies that carefully control for the type of processing required for novelty detection suggest that what may appear as contextual 'what-where' encoding early in infancy may rather reflect encoding of an inflexible, compound representation (Edgin et al., 2014; Gomez & Edgin, 2016; Robinson & Pascalis, 2004), and that proper contextual 'what-where' memories may not emerge until around the end of the second post-natal year (Edgin et al., 2014; Robinson & Pascalis, 2004). This pattern agrees with findings from Newcombe and colleagues (2014) who had children learn the location of a distinctive toy in two different rooms. Newcombe et al. found that 21-26month old children, if presented with a cue, were able to identify the correct container containing the toy for a given context, whereas 15-21month old children tended to search in both containers that were rewarded in either context (Figure 2.2A). The authors also noted significant improvement in the ability of older children (3-5years) to discriminate between the two contexts, with near ceiling performance on this simple task observed at 5 years of age. Thus, 'what-where' encoding displays an inflection point at ~2 years of age in humans.

Although less is known about the development of contextual 'what-where' encoding in NHPs, much attention has been paid to its development in rodents. To study contextual encoding, rodent researchers have traditionally used contextual fear conditioning (CFC) paradigms. In these tasks rodents are placed into a neutral environment where they experience a series of (mild) electric foot shocks. To determine if the rodent has learned the contextual association, the experimenter places the pup back into the environment after some delay and assesses if the pup freezes upon re-exposure (Figure 2.2D). A number of studies have found that contextual encoding measured in this way is already apparent in the pre-weanling period (Akers et al., 2012; Campbell & Campbell, 1962; Guskjolen et al., 2018), with the earliest onset having been reported at P13 (Akers et al., 2012). However, recent evidence suggests that these early emerging contextual memories may lack specificity, and that precise, adult-like contextual associative encoding does not emerge until the fourth post-natal week (A. I. Ramsaran et al., 2023).

Similar findings have been observed in object-context recognition (OCR) studies. In these studies rodents are presented with a pair of identical objects in one environment and another object pair in a second environment. At testing the animals are presented with one contextually familiar object (explored in that environment before) and one contextually novel object (explored in a different context). Preferential exploration of the contextually novel object is interpreted as a measure of successful object-context encoding (Figure 2.2C). Using this procedure, Ramsaran and colleagues (2016) found evidence for object-context

encoding at P17 (Ramsaran, Westbrook, et al., 2016). However, these results are at odds with Asiminas et al. (2022) who only found novelty preferences on the OCR task in pups in the fifth postnatal week (Asiminas, Lyon, et al., 2022). Although the reason for these discrepant results remains to be ascertained, there were notable methodological differences between the two studies. For Ramsaran et al. context meant a completely different environment, located in a different room, with different set of local and distal cues, whereas Asiminas et al. altered the floor and wall texture/colour exclusively. Indeed, Ramsaran and colleagues showed that the ability to encode object-context associations when context is only defined in terms of the location or distal cues displays a significantly later inflection point (P26).

Thus, akin to contextual fear conditioning studies, the OCR studies suggest that the ability to form precise contextual associations emerges only in the post-weaning period, likely during 4th and 5th postnatal week, a developmental timepoint comparable to that observed in humans. See Figure 2.2E for a summary developmental timeline of contextual 'what-where' encoding.

Spatial 'what-where' encoding

Early studies using VPC paradigms suggested that the encoding of spatial location of an object on a visual display was already mature in infancy (Koski et al., 2013; Richmond et al., 2015). Similar observations have been noted in spatial location VPC studies carried out in NHPs (Blue et al., 2013). However, the robustness of this early emerging 'what-where' spatial encoding has been brought into question. It is unclear if novelty preferences observed in human and NHP infancy reflect 'what-where' processing within an allocentric reference frame, or whether they could be accounted for by simpler egocentric or fused (treating the object-background stimulus as a unified scene) encoding strategies (Koski et al., 2013).

Studies that have specifically investigated the ontogeny of allocentric spatial encoding, suggest a later inflection point. At ~2years of age children start being able to use landmarks to guide their search for a reward in an open arena (Newcombe et al., 1998; Ribordy et al., 2013) (Figure 2.3A), a hallmark of allocentric spatial encoding. Similarly, by 9months of age do NHPs show the ability to use landmarks to guide their search for food in an open arena (Lavenex & Lavenex, 2006). Thus, both humans and NHPs display a relatively late inflection point for allocentric, spatial 'what-where' encoding and this inflection point mirrors that observed for adult-like contextual encoding.

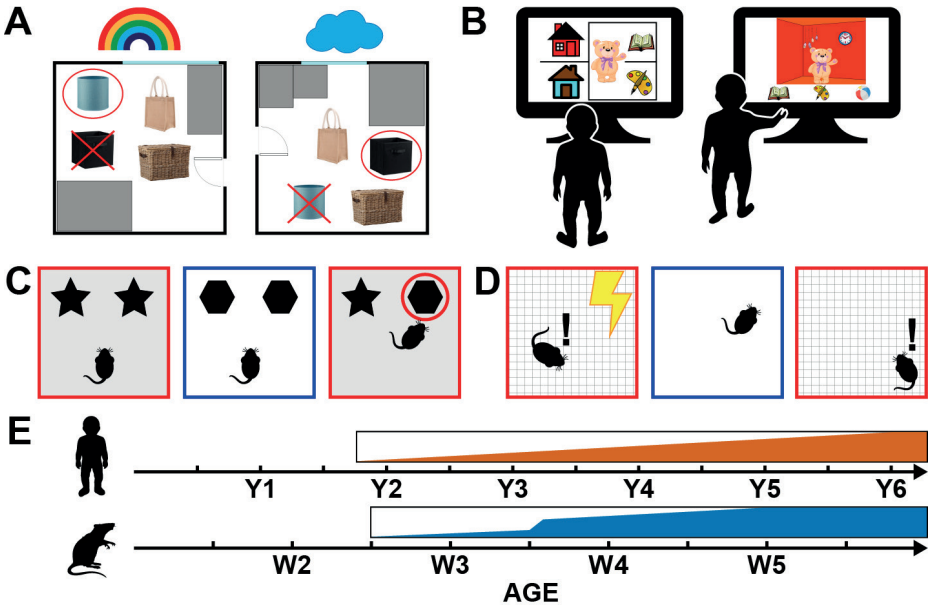

Figure 2.2. Development of contextual 'what-where' encoding. (A) Schematic of the contextual memory task used in (N. S. Newcombe et al., 2014), **(B)** multi-item contextual memory task (Ngo et al., 2018), **(C)** object-context recognition, **(D)** contextual fear conditioning. **(E)** Developmental timeline of human, and rodent contextual encoding.

Comparable observations have been reported in rodent development. The ability to recognise a displaced object in a familiar environment (object-location recognition (OLR) task) has been observed during the third post-natal week (Cruz-Sanchez et al., 2021; Travaglia et al., 2018), before mature contextual 'what-where' encoding. However, a version of the OLR task – so-called object-place recognition (OPR, Figure 2.3E) – which requires more robust object-location associative encoding (the location in which an object appears is not novel, but the conjunction of a particular object in a particular place) displays a later inflection, with novelty preferences on the OPR test first reported at 4 weeks of age (Ainge & Langston, 2012). Similarly, studies assessing the development of the ability to locate a hidden escape platform in a murky pool using landmark cues (watermaze (R. G. Morris et al., 1982), Figure 2.3D) have shown that this capability only becomes adult-like at ~4-weeks of age (Akers et al., 2009; Akers et al., 2007; Rudy et al., 1987). Some studies have observed an earlier emergence of allocentric 'what-where' memory in the watermaze (Guskjolen et al., 2017). However, when the strategies used by developing rodents to encode the location of the escape platform are methodically assessed, it seems the early emerging 'what-where' spatial encoding in the watermaze is likely supported via the encoding of local cues and/or the

implementation of a directional strategy rather than a landmark guided, allocentric strategy (Akers et al., 2009; Akers et al., 2007).

Thus, spatial 'what-where' encoding also emerges in tandem with precise contextual 'what-where' encoding in rodents (see Figure 2.3F for a summary timeline of spatial 'what-where' encoding development). However, as important inflection points seem to only occur at 4 weeks of age in rodents, this may suggest that this form of W-W-W encoding matures at a relatively later age in rodents compared with humans and NHPs. Alternatively, the age of this inflection point could be influenced by the late development of the rodent visual system, which does not become adult-like until 6–7 weeks of age (Fagiolini et al., 1994). Indeed, visual acuity is known to affect performance on the watermaze in adult rats (Prusky et al., 2000). Perhaps future studies can investigate the development of allocentric encoding using cues that draw on the early developing senses, such as audition or olfaction, such that the ontogeny of allocentric encoding can be more readily compared in different mammalian species.

Multi-item 'what-where' encoding

The ability to bind multiple objects to a given contextual and spatial location continues to grow in complexity after single item 'what-where' encoding has emerged. Ngo and colleagues had 4- and 6-year-old children watch cartoons in which different houses contained pairs of items that varied by context, e.g. "A bear in the red house is holding a painting palette but in the blue house it is holding a book". Following the encoding session, the children were shown one of the two contexts containing only the overlapping item (e.g., bear in the red house). The children's task was to correctly identify which item the bear had been paired with in that context (painting palette). Importantly, among the items the children could choose from was a lure (book) as well as foils (e.g. ball) (Figure 2.2B). Ngo and colleagues found that 6-year-old children were significantly better at discriminating between target and lure items compared to 4-year-olds. Indeed, 4-year olds' ability to reject lures did not differ from chance, while their memory for individual items was relatively intact (Ngo et al., 2018). In the spatial domain, Ribordy and colleagues (2013) showed that between the ages of 3 and 5 children start being able to encode the locations of multiple rewards in an open arena within an allocentric reference frame(Ribordy et al., 2013) (Figure 2.3B), similar to results obtained by Overman and colleagues (Overman et al., 1996). Thus, the ability to form complex 'what-where' memories – where multiple items need to be bound to their context or allocentric spatial location - undergoes significant development between the ages of 4 and 6.

NHP primate studies have also observed a late inflection point for multi-item 'what-where' binding. Blue et al. (2013) found novelty preference on the object-in-place VPC task – where monkeys need to encode the spatial location of multiple objects in an array - only emerges near the end of the second postnatal year (J. Bachevalier, unpublished data) (Figure 2.3C). These studies suggest that multi-item binding emerges relatively late in NHP development as it does in human development. We know of no rodent study that has charted the ontogeny of multi-item 'what-where' encoding.

The improvements in 'what-where' contextual and spatial encoding observed may reflect development in the resolution of the memory representation. Ngo and colleagues (2019) showed that accurate discrimination of two contextually similar memories did not differ between 4- and 6- year olds, but performance was lower compared to adults (Ngo et al., 2019). Similarly, Lambert and colleagues (2017) showed that the ability to discriminate between nearby spatial locations and temporally close memories improved between the ages of 3.5 and 7.

In sum, a hallmark of episodic-like memory encoding development may be the emergence of the ability to form complex and specific 'what-where' memories. This suggestion agrees with contemporary theories of episodic memory development that posit that one of the key changes to cognition early in life is the emergence of pattern separation (A. Keresztes et al., 2018; Ngo et al., 2018; Ramsaran et al., 2019) which supports orthogonal encoding of individual but overlapping memories (Marr, 1971).

2.2.3 The development of 'what-when' and 'what-where-when' encoding

The emergence of 'what-when' binding in W-W-W memory as well as the full 'what-when-where' encoding triad has been studied less systematically. When studying the encoding of time in W-W-W memory, researchers often assess the ability of developing children to encode the order or sequence in which events occur. One test of temporal encoding is the 'hide and seek' test used by Hayne and Imuta (2011). In their study, 3- and 4-year-old children observed an experimenter hide three distinct toys in different rooms in their house. At testing, 5 minutes later, the experimenter asked the children to tell them in what order they had entered the different rooms (Figure 2.4A). The authors found 3-years-olds performed significantly worse than 4-year-olds, suggesting 'what-when' encoding develops significantly during this age period. Similarly, Mastrogiuseppe and colleagues (2019) found that 'what-when' memory (order in which objects were placed) develops particularly late (6- 8 years of age), and that its emergence coincides with the development of

'what-where-when' memory (knowing the order as well as spatial location of objects) (Mastrogiuseppe et al., 2019). However, testing took place after a delay, making it hard to determine if the late emergence of 'what-when' and 'what-where-when' memory reflects the inability to encode such associations or the delayed development of memory retention.

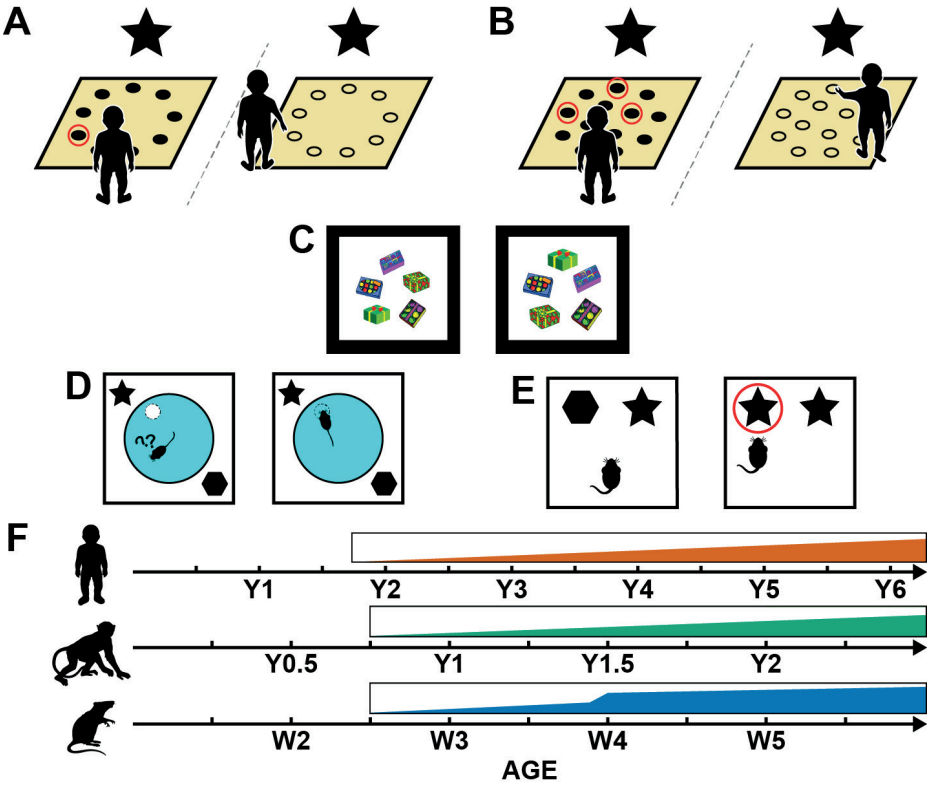

Figure 2.3. Development of spatial 'what-where' encoding. (A) Schematic of landmark-guided spatial memory test, **(B)** object-place recognition paradigm, **(C)** object-in-place VPC, **(D)** the watermaze, **(E)** object-place recognition paradigm, **(F)** Developmental timeline of human, NHP and rodent spatial 'what-where' encoding.

However, early studies using deferred imitation (Piaget, 1952) to study the development of temporal encoding - where infants/toddlers observe an adult perform a sequence of actions and are then tested for their memory of the action sequence – have shown a relatively early inflection point. Successful encoding of arbitrary action sequences has been observed in the second year (P. J. Bauer et al., 1998). VPC studies assessing memory for temporal order – where children watch familiar movie clips whose temporal sequence has been scrambled – have observed an

even earlier inflection point. Sonne and colleagues found evidence for 'what-when' temporal encoding in infancy (down to 6-months of age) (Sonne et al., 2018a, 2023). Although the reasons for these discrepant findings remain to be ascertained, Sonne et al. showed children clips that displayed scenes whose normal temporal order is dictated by physics (e.g. jumping up and down). Thus, novelty preferences in the scrambled clips could have been influenced by the fact that these clips violated the infants understanding of the order in which events occur in the world. Indeed, Benear and colleagues showed that memory for temporal order in complex events develops significantly between the ages of 4 and 7 (Benear et al., 2023).

The ontogeny of 'what-when' and 'what-where-when' memory in non-human animals has received relatively little research attention. This likely reflects the difficulty in assessing temporal encoding in non-human animals. However, researchers have used the so-called object-place-context recognition (OPCR) memory test as a proxy to study such 'what-where-when' encoding in rodent development. In the OPCR test rodents not only have to learn to associate an object with a spatial location, but also a particular context (see Figure 2.4B). Context in these paradigms has been argued to represent a form of temporal encoding (Asiminas, Lyon, et al., 2022). Two studies have attempted to chart its ontogenetic emergence. Asiminas and colleagues found this encoding triad in the rat emerged at ~7 weeks of age, while Ramsaran and colleagues (2016b) observed an inflection point in 5th post-natal week (Ramsaran, Sanders, et al., 2016). Again, methodological differences in how context was defined may explain these discrepant results – different rooms vs changes to the colour and texture of walls and floor. Further, Asiminas and colleagues tested the pups on other object recognition tests prior to the OPCR test, which may have caused interference. In any case, these studies provide the first indication that 'what-where-when', episodic-like encoding may emerge ~5-7weeks of age in rodents. See Figure 2.4C for a summary timeline of 'what-when' and 'what-where-when' encoding development.

It should be highlighted that paradigms for studying 'what-where-when' memory have been developed for non-human animals, such as food caching birds (for a review see (Griffiths et al., 1999)) and apes (Martin-Ordas et al., 2010). Clayton and Dickinson (1998) showed that scrub jays cannot only remember where particular foods (peanuts or worms) were located after a single caching event but were also able to integrate information about time since caching when allowed to recover their cached items (Clayton & Dickinson, 1998). A similar paradigm has been adapted to chimpanzees, which show a similar capability for 'what-where-when' encoding (Martin-Ordas et al., 2010). We encourage the memory development research community to develop comparable paradigms that are suitable for rodents.

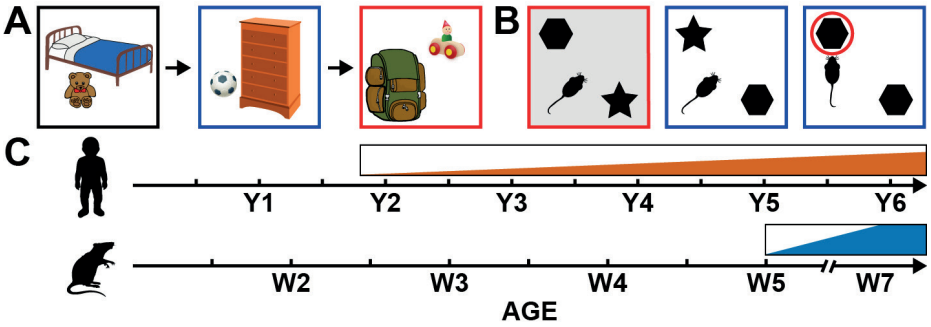

Figure 2.4. Development of 'what-where-when' encoding. (A) Schematic of the 'what-where'-when' memory tasks used in (H. Hayne & K. Imuta, 2011), **(B)** object-place-context paradigm. **(C)** Developmental timeline of human and rodent 'what-where-when' encoding maturation.

2.3 Development of episodic-like retention and retrieval

The previous discussion has concentrated on W-W-W encoding. Now we shift to discussing the development of the ability to retain new memories over time and the development of retrieval processes.

2.3.1 The development of episodic-like memory retention

VPC studies, which have investigated the emergence of the 'what' element in W-W-W memory, show that object novelty preferences can be observed in 3-6 months old infants at short (24 hours) delays. Further, Fagan (1973) found that infants 6-months of age already display novelty responses with a 2-week delay between presentation and testing (J. F. Fagan, 3rd, 1973). Using familiarity preferences as a measure of memory over longer delays, Bahrick and Pickens (1995) observed memory over a 3-month period in 3-month-old infants (L. E. Bahrick & J. N. Pickens, 1995). In rodents, OR tasks have shown memory retention at 2-and 24-hour delays at the start of the fourth postnatal week (Anderson et al., 2004; Cruz-Sanchez et al., 2021), although one study observed intact OR recognition memory at P17 (Power et al., 2023). These data suggest retention of simple 'what' memories may emerge relatively early in human and rodent development. Memory retention has not been systematically tested in NHPs (but see (Lavenex & Lavenex, 2006) as such the developmental trajectory of this aspect of 'what-where-when' memory in NHPs remains to be elucidated.

Less is known regarding the development of retention for associative W-W-W memories. Deferred imitation studies have shown that retention of arbitrary action sequences over a 2-week period is present at the start of the third post-

natal year (Bauer et al., 1998). Benear and colleagues showed that retention at 24hrs was present at the time when 'what-where' multi-item contextual binding emerges (~4years of age) (Benear et al., 2021), although memory performance was notably weaker in 4-year-olds after a delay. Further, Saragosa-Harris (2021) found that contextual 'what-where' memory at long delays (1 week), although present, was notably weaker in 3-year olds compared to 5-year olds (Saragosa-Harris et al., 2021a). This pattern is in agreement with the results of Scarf et al. (2013) who studied retention using the so-called spoon test – a test proposed by Tulving (Tulving et al., 2005) as a non-verbal test of episodic memory in children. In their study, children's ability to encode and recall an object (key) association with a play event (treasure hunt) was tested. Scarf et al.(2013) found intact retention at 24-hour and 1-week delay in 4-year olds, while 3-year olds only showed retention at short (up to 30min) delay. Overall, questions remain regarding the ontogenetic timeline of W-W-W memory retention in humans, given the paucity of systematic studies.

This topic has not been studied extensively in NHPs, but there are rodent studies. For example, Travaglia and colleagues (2016) tested contextual 'what-where' memory retention using a CFC paradigm. They found that P17 mouse pups tested 24hours after encoding showed no memory of the learned association while P24 pups did (Travaglia et al., 2016). In another study Travaglia et al. found object location memory at a 2-hour delay only at P24 and not P17 (Travaglia et al., 2018). Similarly, Ramsaran and colleagues (2023) found robust 'what-where' retention at 24hours in P24 pups (Adam I. Ramsaran et al., 2023) (similar to (Anderson & Riccio, 2005)). However, others have found evidence for contextual as well as spatial 'what-where' memory during the third post-natal week (from P15) (Akers et al., 2012; Guskjolen et al., 2017; Power et al., 2023).

These contradictory findings, both in the rodent and human literature, may be explained by two factors: encoding specificity and retrieval processes. In rodent studies, the specificity of the retained spatial/contextual 'what-where' memory is not always explicitly tested. For example, if testing contextual 'what-where' retention using a CFC paradigm, studies do not routinely place the pups into a neutral environment just after the encoding session to ascertain that the learned association is specific to the shock environment. Although this has been done in some cases at memory testing 24hours after encoding (e.g. (A. I. Ramsaran et al., 2023)), not assessing the specificity of the contextual association just after encoding makes it hard to interpret any absence of retention. That is, immaturity of contextual 'what-where' retention could simply reflect immaturity of encoding. Somewhat similar arguments can be made for the reported early emergence of

spatial 'what-where' retention using the watermaze (Akers et al., 2012). As research has shown that encoding on this task may not be allocentric in younger pups (P20-21) (Akers et al., 2009), the early emergence of retention found may not reflect the emergence of allocentric spatial memory, but rather retention of egocentric spatial memories.Indeed, adult-like allocentric encoding has only been reported at P26-27 (Akers et al., 2009). Thus, it may be concluded that long-term 'what-where' memories emerge during the fourth post-natal week in rodent development.

Concerns about encoding specificity may not readily apply to the discrepant results observed in the human literature, as appropriate encoding controls conditions are often employed (Benear et al., 2021; Saragosa-Harris et al., 2021a; Scarf et al., 2013; Sonne T et al., 2023; Sonne et al., 2018b). To reconcile these differences, one may need to consider retrieval processes. Studies that assess associative memory retention via novelty preferences on the VPC task are thought to only require recognition memory – the animal just has to recognise that they have seen stimuli before (Figure 2.5A). Other studies require children to explicitly express a learned W-W-W memory, i.e., to recall a stored memory from long-term memory. Hence, we now turn to examine different retrieval processes.

2.3.2 The development of episodic-like retrieval processes

VPC studies suggest that recognition-mediated memory retention of certain types of W-W-W memories mature early, perhaps being present in the second half of the first post-natal year (Bahrick & Pickens, 1995; Fagan III, 1973). However, studies that require children to explicitly recall a memory suggest that memory retention develops notably later (between the ages of 3 and 8 (Mastrogiuseppe et al., 2019; Saragosa-Harris et al., 2021a; Scarf et al., 2013)). Adult-like (autonoetic) recall has not been studied extensively. However, autonoetic recall of personal events experienced at age 5 and tested between the ages of 6 and 11 years seems to improve with age (Picard et al., 2009). Older children were more likely to say they remembered an event they recalled vs just knowing it occurred – a defining feature of autonoetic recall (E Tulving, 1985). Further, older children also gave more contextualised descriptions of their recalled memories and needed fewer cues to elicit recall. Thus, autonoetic recall may develop particularly late, undergoing significant development during the school years. In agreement, studies assessing source recognition in children (i.e. explaining how one knows something) also significant development between the ages of 3 and 6 (Gopnik & Graf, 1988; Perner & Ruffman, 1995).

A further distinction may be made between strategic vs spontaneous recall. Strategic recall tests simply involve asking what a child remembers about an event (Figure 2.5C). These tests place additional cognitive demands on the child, as they need to conduct a cognitive search for the correct memory. In other words, strategic recall requires mature executive function as well as mature memory trace recall. Spontaneous recall, on the other hand, is less cognitively demanding and is simply thought to arise via an associative process (Figure 2.5B).

Interestingly, recent research suggests that spontaneous recall may develop early(Krøjgaard et al., 2022; Leichtman, 2006). Leichtman (2006) had children aged between 4 months and 3 years engage in a play event. The children returned to the lab 3-6 months after the learning episode. Leichtman found that children as young as 16-17 months of age spontaneously recalled their previous visit to the lab. Further, a series of subsequent experiments by Krjøgaard and colleagues (Krojgaard et al., 2014; Krojgaard et al., 2017; Sonne et al., 2019) showed that spontaneous recall is also present for events experienced only once. In their studies, Krjøgaard et al. had children aged 3-4 engage in a play event. On a subsequent visit, occurring at least one week later, spontaneous retrievals of the encoding event were recorded by an experimenter. Importantly, on the second visit the children were not shown the toys they had played with on their first visit, but were simply placed back into the same room. Krjøgaard et al. noted that 30-60% of children displayed spontaneous recall for their first visit and no age-related differences were observed. Importantly, when explicitly asked to recall their visit, a striking distinction in performance was observed between the younger and older children with the older children outperforming younger children.

Taken together, these studies suggest that spontaneous recall may mature before strategic recall. Specifically, spontaneous recall may be mature by age 3 at least, when strategic recall is still relatively immature. Thus, perhaps the late emergence of recall observed in multiple studies (e.g., (Scarf et al., 2013), (H. Hayne & K. Imuta, 2011), and (Mastrogiuseppe et al., 2019)) could be due to the fact that these studies required strategic recall.

Differentiating between different forms of retrieval is not straightforward in non-human animals. However, spontaneous recall has been documented extensively in apes (Lewis et al., 2019). For example, when orangutans are placed back into an environment where they had found tasty treats hidden two weeks earlier and are presented with a distinctive cue of the learning event (food crumbs) they immediately search for the food (Lewis et al., 2019). Thus, perhaps animal

researchers can differentiate between memory retrieval processes by assessing if memory requires an execution of a goal directed behaviour (running to a previously rewarded location), which may reflect spontaneous recall processes, or whether it need only be expressed via novelty-related behaviours (e.g. preferential exploration of an object), which may reflect the engagement of recognition processes.

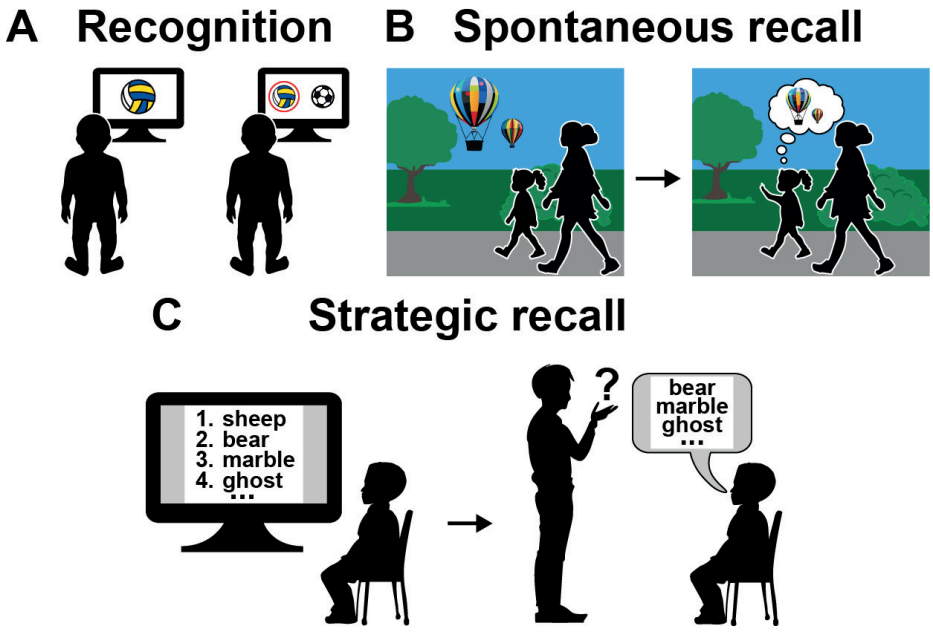

Figure 2.5. Development of memory retention and retrieval mechanisms. (A) Schematic of a recognition, **(B)** spontaneous recall, and **(C)** strategic recall paradigms.

2.4 Development of the neural substrates and mechanisms for episodic memory

Here, we will give an overview of studies that have charted the morphological and physiological development of the neuronal substrates implicated in episodic memory. We will first discuss the core brain regions thought to support episodic memory development, then we will review the key morphological and neurophysiological developmental milestones observed in the early life period. For more detailed reviews on cellular and molecular development we refer the reader to a number of excellent recent reviews on the topic (Alberini & Travaglia, 2017; R. Cossart & R. Khazipov, 2022; Donato et al., 2021; Donato et al., 2023; Travaglia et al., 2018).

2.4.1 Neural substrates of episodic-like memory ontogenesis

In human adults, episodic memory is known to depend critically on the hippocampal formation (Scoville & Milner, 1957). Seminal research has shown that injury incurred to the hippocampus early in life causes specific deficits to 'what-where-when' memory function (Blue et al., 2013; Freeman & Stanton, 1991; Vargha-Khadem et al., 1997). Vargha-Khadem and colleagues showed that hypoxic ischaemia suffered in the peri/neo-natal period, that results in selective hippocampal atrophy (Loïc J. Chareyron et al., 2023; Gadian et al., 2000; Vargha-Khadem et al., 1997), leads to a selective cognitive impairment to episodic memory ('developmental amnesia'). These individuals struggle to recall everyday events and special occasions, while general cognitive ability (language skills, factual knowledge, etc) is relatively preserved (Elward & Vargha-Khadem, 2018b). The memory capabilities of DA patients have been extensively studied. These studies have shown that DA patients can form simple item ('what') memories, and even some forms of 'what-where' spatial memories (Allen et al., 2022; Elward et al., 2021), although they seem to have a specific deficit in 'what-where' encoding that requires an allocentric representation (King et al., 2004) as well as temporal ('what-where-when') encoding (Vargha-Khadem et al., 1997). Furthermore, their deficit in memory retention seems to be mediated via an inability to retrieve memories via autonoetic recall. If memory retention is tested via recognition memory tests (e.g. multiple choice), DA patients often perform comparably to controls(Adlam et al., 2005; Elward et al., 2023) (see Box 1 for a further discussion of DA and its implication for developmental neuroplasticity). Thus, the hippocampus seems critical for the development of allocentric 'what-where' and 'what-where-when' encoding, as well as recall, while the development of 'what' and egocentric 'what-where' memories, particularly when accessed via recognition processes, may be less dependent on the hippocampus.

These results largely agree with lesion studies carried out on rodents and NHPs. Neonatal lesions to the NHP hippocampus have been found to impair the ontogenetic emergence of allocentric 'what-where' memories, such as those tested via the object-in-place VPC task (Blue et al., 2013). Neonatal hippocampal lesions do not impair object ('what') memory VPC learning, when this is tested within the first post-natal year. However, when tested at 18months of age, these neonatally hippocampal-lesioned NHPs, as well as those whose hippocampi were lesioned in adulthood, show marked impairment relative to sham-operated monkeys (Blue et al., 2013). This suggests that the neuronal substrates supporting this building block of episodic-like memory undergoes significant reorganisation during the first post-natal year in NHPs. Early in life, object recognition may be supported by perirhinal and parahippocampal cortices (Bachevalier & Nemanic, 2008; Zeamer et al., 2015),

allowing infant NHPs to encode the 'what' in W-W-W associative memory despite the absence of the hippocampus, whereas later in life such memory requires the hippocampus (Nemanic et al., 2004).

Rodent lesion studies have also shown that the emergence of associative 'what-where' spatial memory, as measured by the ability to learn a spatial alternation rule on the T-maze (Freeman & Stanton, 1991) or to recognise a spatially displaced object (Kruger et al., 2012), depends on the hippocampus early in life. Lesioning the hippocampus in the neonatal period has been found to abolish the development of these forms of 'what-where' memory (Freeman & Stanton, 1991; Kruger et al., 2012). Similar findings have been observed for 'what-where' contextual memory development (Foster & Burman, 2010; Raineki et al., 2010).

In addition to the hippocampus, episodic-like memory development may also involve the PFC as neonatal hippocampal lesions have been found to influence the structural development of the PFC in NHPs and rodents (Kruger et al., 2012; Meng et al., 2016; Meng et al., 2014). In Box 3 we elaborate further on the potential role of the PFC in memory development.

2.4.2 Structural development of the neuronal substrates for episodic-like memory

Converging evidence, obtained from different species, point to a protracted structural development of the hippocampus. The volume of the hippocampus is known to double in the first two years of human life (Ellis et al., 2021; Uematsu et al., 2012) with continued growth in the subsequent years (Jabès & Nelson, 2015), and possibly into early adolescence(Uematsu et al., 2012). However, the different subfields – cornu ammonis fields 1-3 (CA1-3) and dentate gyrus (DG) (Figure 2.6A) - of the hippocampus are thought to develop at different rates, with area CA2 likely being relatively mature at birth, while the CA1, CA3 fields and DG develop significantly in the post-natal period (Jabès & Nelson, 2015). The development of DG is known to be particularly protracted, lasting into the second post-natal year at least(Seress et al., 2001; Seress & Mrzljak, 1992). Recent volumetric measurements of the DG and CA fields indicate that CA3 and DG may continue to develop in size until early adulthood (Keresztes et al., 2017).

Stereological studies on developing NHPs and rodents have revealed similar sub-field developmental gradients. The volume of the NHP CA1 has been found to be relatively mature by 6 months of age while DG and CA3 continue to develop until the second post-natal year, at least (Jabes et al., 2010, 2011). Up to 40% of

hippocampal DG neurons are born postnatally in NHPs (Jabes et al., 2010, 2011). Peaks in neurogenesis occur in the postnatal period in rodents (Snyder, 2019). Donato and colleagues (2017) also showed that of all the rodent hippocampal subregions, DG seems to be the last to develop (Donato et al., 2017). Research in non-human animals has also highlighted developmental changes within subregions. For example, the volume of distal CA3 (closer to CA2) becomes adult-like before proximal CA3 (closer to DG), with the volume of distal CA3 being relatively mature at birth whilst the proximal CA3 continues to mature beyond the first post-natal year in NHPs (Jabes et al., 2011). Similar results have been observed in rodents. Distal CA3 neurons are born earlier than proximal CA3 neurons and enter into the hippocampal circuit at an earlier developmental stage (Caviness, 1973). Of note, the distal CA3 receives direct innervation from the EC, whereas proximal CA3 is more extensively innervated by the later maturing DG (Witter MP & DG., 1991).

Within CA1, NHP stereological studies have shown the sub-layer stratum lacunosum-moleculare (SLM) receiving direct projections from layer three of the entorhinal cortex (ECIII) matures before the other sub-layers (stratum radiatum/pyramidale/oriens), which are preferentially targeted by CA3 afferents (Jabes et al., 2011) as a part of the tri-synaptic loop. Specifically, SLM reaches adult-like volume by 3-months of age in NHPs, whereas the other layers develop through the first post-natal year. Rodent studies have observed a deep-to-superficial gradient for neurogenesis and migration in CA1. Namely, deep cells are born and migrate earlier than superficial neurons (Caviness, 1973). Although the cell bodies of the later maturing superficial CA1 cells are located closer to the early maturing sublayer of CA1, electrophysiological studies in adult rodents have shown these cells are preferentially targeted by the late maturing CA3 fibers (Navas-Olive et al., 2020; Valero et al., 2017).

Together these results suggest that the maturation of the hippocampal CA fields may be shaped by the maturation of their dominant inputs. With areas receiving direct projections from ECIII maturing before areas that receive more input via the tri-synaptic pathway (see Figure 2.6E for a timeline for morphological development in the hippocampus).

2.4.3 Development of the neurophysiological mechanisms for episodic (-like) memory

In recent years, significant methodological advances have been achieved that now allow researchers to image the developing human brain. These studies have highlighted that the hippocampus may support episodic-like memory early in

the post-natal period. Prabhakar and colleagues (2018) imaged brain activity via functional magnetic resonance imaging (fMRI) in 2-year-old toddlers during sleep. During scanning, sounds associated with a previous encoding session (playing with a soft toy) were played. Prabhakar and colleagues observed increased hippocampal activity in response to the presentation of the learned song versus a novel song (Prabhakar et al., 2018). Further, the amount of hippocampal activity correlated with the children's recall accuracy of the toy-sound association, tested before the scanning session (see also (Mooney et al., 2021)). Interestingly, hippocampal activity was also observed when testing occurred several months after initial encoding, despite the children not being able to recall the toy-sound association (Johnson et al., 2020). Ellis and colleagues (2021) found the hippocampus to be engaged while infants as young as 3-months-old observed temporally ordered visual stimuli (Ellis et al., 2021). However, they did not test memory.

A dissociation between hippocampal activity and the ability to recall 'what-where' memory has also been noted in DA (Elward et al., 2021). Elward and colleagues had DA patients learn word-scene associations and then tested them on their 'what-where' memory (via a recall test) before a fMRI scanning session. The authors found that, despite the DA patients displaying poor associative recall, the presentation of the paired scene elicited hippocampal activity similar to controls. Overall, it appears likely that, although the hippocampus undergoes significant maturation in the early post-natal period, it may still support elemental W-W-W memory function.

Neurophysiological research in developing rodents, carried out over the past decade, has started to elucidate the ontogeny of hippocampal neuronal mechanisms which may give insight into this early involvement of the hippocampus in W-W-W memory. Below, we summarise core findings from this research. Electrophysiological studies in rat neonates (post-natal weeks 1-2) have shown that major hippocampal oscillations, namely, theta (6-12Hz) and gamma (30-100Hz) (Buzsaki, 2010; Buzsaki & Tingley, 2018; Drieu et al., 2018; Harris et al., 2003) are already present by two weeks of age, yet they continue to increase in frequency and power during the third and fourth postnatal week (Brockmann et al., 2011; Lahtinen et al., 2002; Leblanc & Bland, 1979; Wills et al., 2010). Sharp-wave ripple oscillations (SWRs) display a more protracted emergence. The sharp wave component – originating from synchronous activity in CA3 - may emerge in the first post-natal week (Leinekugel, Khazipov, Cannon, Hirase, Ben-Ari, & Buzsaki, 2002; Valeeva et al., 2019) whereas the high frequency ripple component – reflecting population activity bursts in CA1 - has only first been recorded at ~2weeks of age and continues to develop in power until the end of the third postnatal week (Buhl & Buzsaki, 2005). Thus, by 3-4 weeks of

age, major hippocampal oscillations that orchestrate information processing in hippocampal circuits seem to have matured to near adult-like levels.

Furthermore, several studies have charted the development of hippocampal spatially tuned neurons ("place cells") in rat pups. Principal cells of the CA regions of the adult hippocampus display spatially confined activity during locomotory periods encoding allocentric relations between an animal's current location and landmarks/ environmental boundaries (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). Place cells with similar functional tuning (or "spatial view cells") have been observed in humans and NHPs (Ekstrom et al., 2003; Hori et al., 2005)). Hippocampal place cells can be recorded, in the rat, from P16. However, their stability as well spatial specificity continues to mature until at least the end of the fourth postnatal week (Langston et al., 2010b; Langston & Wood, 2010; Martin & Berthoz, 2002; Scott et al., 2011; Wills et al., 2010). Interestingly, around the time grid cells from ECII emerge (~P20) (Langston et al., 2010b; Wills et al., 2010) (which provide place cells with spatial input), place cells start to form more stable spatial firing fields in the centre of open-field environments. Prior to this age, place cells are only stable around environmental edges. Furthermore, Muessig and colleagues (2016) showed that although place cells in the pre-weanling (<P21) period remap (alter where or whether they fire at all) between different environments, remapping seems to be driven by olfactory cues in the preweaning period, and only in the fourth post-natal week do place cells start to integrate multiple sensory cues (Muessig et al., 2016). It should be noted, however, that integration of more subtle sensory cues (such as floor texture) is still not apparent in the early post-weaning period (beginning of 4th post-natal week) (Muessig et al., 2016). Thus, although place cells are present during the third post-natal week, their stability and ability to integrate multi-sensory cues extends at least until the end of the fourth post-natal week.

The development of hippocampal "replay" (Figure 2.6C) – time-compressed reactivations of CA1 wakeful activity patterns thought to support the commission of new memories to long-term storage (Carr et al., 2011; Diba & Buzsaki, 2007; Foster & Wilson, 2006a; Jadhav et al., 2012; Lee & Wilson, 2002; Wilson & McNaughton, 1994) – has recently received increased attention. Reactivations have been observed as early as P17. However, early reactivations tend to depict confined regions of an animal's environment (Farooq & Dragoi, 2019; Muessig et al., 2019a). It is only during the fourth postnatal week that replays start to tie together sequentially visited locations (Farooq & Dragoi, 2019; Muessig et al., 2019a), akin to what is observed in adult rats. In tandem with the emergence of adult-like, sequential replay, place cells start to show sequentially organised activity within individual

cycles of theta-band oscillations (Muessig et al., 2019a) ("theta sequences", Figure 2.6B). Overall, by the ~4th postnatal week the neural machinery thought to support memory encoding and retention seems to be in place (see Box 3 for discussion of possible links between neuro- and memory development).

Moreover, significant progress has also been made to tracking encoded memory "engrams" (Schacter et al., 1978) during the early post-natal period (Figure 2.6D). These studies capitalise on techniques that allow tagging of neurons active during encoding periods (Guenthner et al., 2013). Using this technique, Guskjolen and colleagues (2017) reported that although contextual associative memories (tested via CFC) encoded at P17 are rapidly forgotten in natural settings, if the original engram is optogenetically reactivated in adulthood, mice display intact recall of the fearful early life event (Guskjolen et al., 2018). Similar results were obtained by Power et al. (2023), who also replicated the effect for object recognition and a cued version of the Barnes maze (where rodents learn the location of an escape hole on a circular platform). Subsequently, Ramsaran and colleagues (2023) have shown that infantile memories are less precise and engrams include more CA1 neurons than in adults. The reduction in CA1 engram size observed in development may reflect the protracted development of inhibition in the hippocampus. Indeed, Ramsaran et al. only observed adult-like inhibition, mediated by parvalbumin (PV) expressing interneurons, during 4th post-natal week and artificially decreasing PV activity in adult animals was found to lead to pup-like, enlarged engrams and poor 'what-where' contextual retention. In sum, by the middle of the fourth post-natal week, memory engrams seem to have matured.

Together, current work suggests that by ~2 weeks of age rudimentary hippocampal function is present, as all major oscillations are present and place cells can be recorded. However, during the subsequent ~2 weeks, hippocampal representations and network mechanisms undergo significant development, with the emergence of adult-like spatial tuning, sparse engrams, and sequential activity patterns (replay and theta sequences, see Figure 2.6F for a summary developmental timeline). We hope the coming years will chart the emergence of these core neurophysiological mechanisms in relation to the gradual emergence of W-W-W memory (see Box 3 for initial speculations).

2.5 Challenges to comparative research

We have described the ontogeny of key cognitive and neurobiological processes that contribute to the gradual development of episodic-like memory. However, several methodological and theoretical issues make it hard to determine

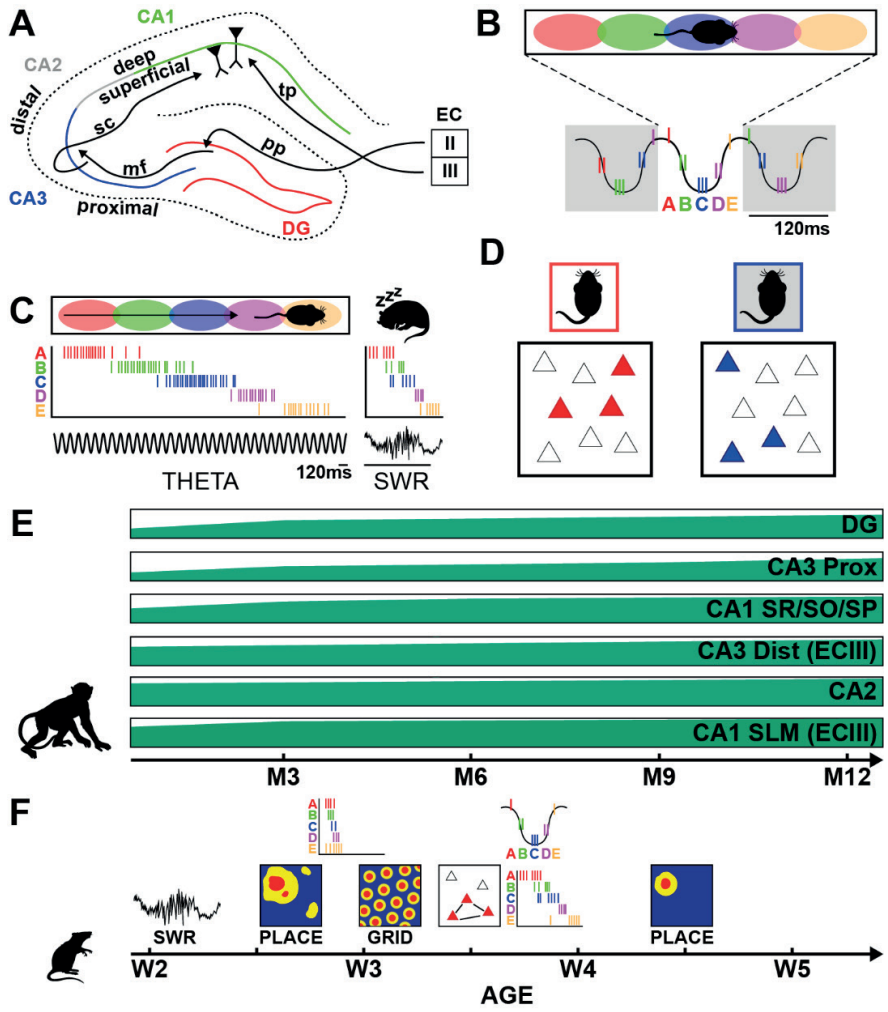

Figure 2.6. Development of hippocampal morphology and neurophysiological mechanisms. **(A)** Anatomical diagram of the hippocampus, its subfields and principal intra and extra-hippocampal projections. **(B)** Schematic of hippocampal theta sequences. Top: Coloured circles represent place fields of individual place cells. Bottom: Spikes from place cells are shown as rasters nested in theta oscillations. **(C)**. Schematic of hippocampal replay. Left: Runs on a linear runway are underpinned by sequential activation of place cells (Top: schematic of place fields on track, bottom: raster plot of place cell activity during a single track traversal). Right: During rest/sleep, place cell sequences observed during wakefulness are spontaneously replayed during sharp-wave ripple events. **(D)** Schematic diagram of memory engram tagging. Top: rodent located in two environments. Bottom: coloured triangles depict engrams for the two environments. **(E)** Morphological maturation of the hippocampal CA and DG fields based on NHP volumetric analysis (Lavenex & Banta Lavenex, 2013). Anatomical development of the rodent and human hippocampal CA and DG fields follows a similar order. **(F)** Developmental timeline of neurophysiological mechanisms supporting memory in rodents. CA1-3=cornu ammonis 1-3, DG=dentate gyrus, EC=entorhinal cortex, mf=mossy fiber pathway, sc=schaffer collaterals, tp=temporoammonic pathway, pp=perforant pathway.

developmental trajectories with precision. Here, we summarise these challenges, and offer potential solutions.

Comparative potential of (memory) tasks. Many neurophysiological studies in rodents have not investigated neuronal maturation in the context of behavioural data on memory development (rodents simply shuttle back and forth on linear runways or forage for food (Langston et al., 2010b; Muessig et al., 2019a; Scott et al., 2011; Wills et al., 2010)). Other studies use tasks that are not implementable in developing humans, such as CFC. Much behavioural research on human children has used paradigms such as the mobile conjugate task (Hartshorn et al., 1998; Rovee-Collier et al., 1999) and deferred imitation(Barr et al., 1996; Barr et al., 2005), which draw on a motor and social repertoire not available to other species. We encourage researchers to use tasks (e.g., VPC, object exploration tasks) that test W-W-W memory and are amenable to cross-species testing.

Measuring encoding success. The success of encoding is not always determined. This complicates interpretations when memory fails at testing, as the failure could either be due to a retention or an encoding problem. Testing memory immediately after encoding would address this problem. Alternatively, in VPC paradigms encoding success can be directly gauged by measuring if looking time reliably decreases to visual stimuli during encoding.

Encoding specificity. A related issue is the specificity of the encoded memory. For example, CFC studies have shown that early in life rodents tend to generalise fear responses to neutral contexts (e.g. (Akers et al., 2012)). Thus, it is essential to test the specificity of the contextual 'what-where' association in CFC tasks, and to do so immediately after encoding. Similarly, tasks that are intended to measure spatial 'what-where' encoding within an allocentric reference frame (e.g. (Blue et al., 2013; Guskjolen et al., 2017)), can often be solved without the use of allocentric strategies (Akers et al., 2009; Akers et al., 2007; Bachevalier & Nemanic, 2008). We encourage experimenters to use robust controls to disambiguate the nature of encoding.

Episodic nature of memory tests. A defining feature of episodic memory is that memories can be formed without extensive sampling ("one-shot" learning (Tse et al., 2007)). Given that definition, it is important to not *over*-familiarise developing animals to study stimuli, in order to ensure that memory for unique events is indeed being tested and to use stimuli configurations/sequences that are not already familiar to the developing animal. For example, encoding sessions should be limited in duration, as is routinely done in CFC and object recognition

studies (e.g. OCR, OPC, OPCR, VPC). However, extensive training is also common – for example in watermaze studies (Akers et al., 2009; Guskjolen et al., 2017), even though one-session paradigms exist for adults (Genzel et al., 2017) and could be optimised for use in developing animals. Furthermore, studies using dynamic visual stimuli (e.g. (Sonne T et al., 2023; Sonne et al., 2018b)), need to consider whether successful memory is influenced by whether the developing animal has been exposed to similar study stimuli in the past.

Relatedly, although CFC tasks are often used as a proxy for episodic memory, they are also known to engage different circuits than non-affective episodic-like memory tasks(Alvarado et al., 2002; LeDoux & Daw, 2018). This raises questions about whether this task accurately provides insight into episodic memory ontogeny. We urge memory development researchers to not exclusively rely on CFC paradigms when studying W-W-W memory development.

Measuring retrieval processes. Retention of episodic-like memories may be supported by different retrieval processes (recognition, spontaneous and strategic recall). However, which retrieval process a memory task draws on is often not explicitly tested. Given the developmental trajectory of memory retention remains relatively unclear, carefully designing memory tests so that they dissociate different retrieval processes may be a useful tool for addressing this caveat in our understanding, as discussed by (Krøjgaard et al., 2022).

2.6 Conclusions and future perspective

Concerted research efforts over the past decades have significantly advanced our understanding of the ontogeny of W-W-W associative memory in different mammalian species and have provided insights into some of the key neurodevelopmental milestones that may support W-W-W memory ontogenesis. However, significant caveats remain. Particularly, we still lack information as to the development of the different retrieval process (recognition, strategic vs spontaneous recall), the different dimensions of episodic memory encoding ('what-when', 'what-where-when'), as well as the relationship between neuronal- and memory development (see BOX 4 for further discussion on knowledge gaps). This last point is particularly pertinent as elucidating this relationship may have significant implications for understanding the neurobiological basis of common neurodevelopmental disorders affecting memory (Down Syndrome, Autism Spectrum Disorder, etc) and impairments observed in the context of early-life brain injury (e.g. developmental amnesia (Vargha-Khadem et al., 1997)).

Linking cognitive and neural development requires closer ties and collaboration between cognitive scientists studying human development and neuroscientists investigating neuronal circuit maturation in non-human animals. Specifically, we advocate for collaborative partnerships between human and non-human animal researchers where memory development can be studied in parallel in multiple species and tasks used to test memory capability are aligned as much as possible. Doing so would be a significant stepping-stone in establishing a comprehensive cognitive-neurobiological model of cognitive ontogeny and would ensure findings obtained via non-human animal research can be generalised to humans and ultimately benefiting society.

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2.8 Supplemental material

2.8.1 Glossary

Episodic memory = Memory for personal events that can be consciously recalled. Episodic memory includes information about what happened where and when (W-W-W).

What-Where-When (W-W-W) memory/episodic-like memory = 'what-where-when' memory where conscious recall cannot be ascertained. Term is commonly used when investigating episodic memory in non-human animals and pre-verbal infants.

Semantic memory = Memory for facts and world knowledge (e.g. knowing Paris is the capital of France vs. remembering your last trip to Paris). Unlike episodic retrieval, retrieval of semantic memories is usually not associated with a felt sense of travelling back to where/when encoding took place.

Encoding = The ability to form a memory trace.

Recognition = The ability to recognise previously encoded stimuli as old without the need to retrieve the encoded memory trace. Recognition is usually thought to be supported by familiarity processes and can be tested via VPC, object recognition and multiple-choice paradigms, although recognition tests may evoke recall processes when deep processing is encouraged during study.

Recall = The ability to retrieve an encoded memory from memory storage. Recall is traditionally tested via free recall (i.e. where subjects are simply asked to freely recall studied stimuli, such as a list of words) but can also be tested via cued recall – where subjects are provided with an incomplete/degraded portion of the original studied material (e.g. a word in a word pair).

Autonoesis = Conscious recall experienced and reported from a first-person perspective. During autonoetic recall the person experiences travelling back in time to retrieve a stored memory.

Pattern separation = The process by which overlapping or similar memories are supported by non-overlapping neuronal representations.

Allocentric memory = Spatial memory encoded in an environment-centric reference frame as opposed to an egocentric reference frame (e.g. the train station is located north of the town hall vs the train station is on my right).

2.8.2 BOX 1: Functional reorganisation in the presence of early hippocampal injury

Developmental amnesia (DA) is a limited form of amnesia resulting from selective, bilateral hippocampal atrophy associated with an early-life hypoxic-ischaemic episode (Loïc J. Chareyron et al., 2023; Dzieciol et al., 2017; Gadian et al., 2000; Vargha-Khadem et al., 1997). Individuals with DA reach age-appropriate developmental milestones across infancy to adolescence for language acquisition, semantic knowledge, motor and educational achievements. However, a profound and chronic delay-dependent deficit in the ability to remember personally

experienced events – including birthday parties, special occasions – usually becomes apparent around or shortly after the preschool years. The memory failures that become apparent are well illustrated by the following anecdote, related to one of the authors (FVK) by the mother of patient Jon – a DA patient whose amnesia has been extensively described (Vargha-Khadem et al., 1997).

"One day, when he was 8-years old, Jon went to the mall with his mother where he saw a woman wearing a sari with a large snake wrapped around her shoulders and arms. Jon was fascinated by the live snake. Noting his interest, the woman asked Jon to approach so he could touch and stroke the snake. Moments later, Jon and his mother left the mall and drove home. Upon entering the house, Jon's mother asked him to "go tell your father what you just saw in the mall". To which Jon responded with a puzzled look on his face: "what did I see?".

One of the most striking aspects of DA, is that in the presence of this profound deficit in episodic recall (via autonesis), the ability to learn facts and world knowledge remains intact and continues to develop with increasing age and cognitive ability. In other words, DA is characterised by a striking dissociation between episodic and semantic memory (Elward & Vargha-Khadem, 2018b; Vargha-Khadem et al., 1997). This dissociation is consistent with influential models of the organisation of explicit memory that posit the two memory systems are dissociable neurologically (Mishkin et al., 1997). Indeed, if a DA patient is asked about events of their daily life, they seldom respond with "I don't remember". Rather, they may give a generic account of events that are plausible to occur (Vargha-Khadem & Cacucci, 2021), suggesting memory encoding and consolidation is at least to some extent preserved in DA.

DA is a prime example of the ability of the developing brain to reorganise in response to injury. A seminal study by Maguire and colleagues (2001) showed that although the DA patient Jon displays, in adulthood, activation of a similar network of brain regions in relation to autobiographical memory recall as controls, the authors also noted some differences. The autobiographical memory network – including the hippocampus, surrounding parahippocampal regions and associated cortices - was less lateralised in Jon compared typically developing individuals. Furthermore, in controls recall was associated with strong functional connectivity between the hippocampus and PFC, while in addition to displaying hippocampal-PFC connectivity Jon also displayed enhanced retrosplenial-hippocampal and retrosplenial-PFC connectivity (Maguire et al., 2001); suggesting memory processes may be less localised in DA.

Recent evidence suggests that the extent of hippocampal damage in DA has a strong influence on the (re-)organization of the medial temporal lobe memory circuit. Specifically, the uncus (the most anterior part of the hippocampus) was found to be relatively preserved as compared to the other regions of the hippocampus (Loïc J. Chareyron et al., 2023), and the degree of sparing predicted memory impairments. Namely, greater preservation of the uncus predicted worse recall (Figure S2.1). These negative correlations suggest that when hippocampal circuits are only partially damaged (uncus preserved), the information flow may persist in the spared hippocampal circuits and results in incomplete, and possibly disruptive information processing (Loïc J. Chareyron et al., 2023). Together with the absence of structural damage in surrounding cortices, these negative correlations could reveal the existence of multiple, redundant information processing routes within the spared hippocampal/cortical areas. These parallel circuits could compete for control and disrupt memory performance. In contrast, greater hippocampal damage might induce greater compensatory reconfigurations in neural circuits and enable other structures, in particular the parahippocampal/entorhinal cortices, to assume important aspects of memory function. Importantly, the compensation is not enough to rescue episodic memory function, but rather may allow semantic memory to mature without the hippocampus, as has been found in DA patients (Vargha-Khadem et al., 1997).

Putative compensatory mechanisms of the immature brain that rescue, and possibly augment (Allen et al., 2022; Jonin et al., 2018), non-hippocampal-dependent mnemonic processes need to be investigated. Some initial insights may be gained from a recent study in a NHP model of DA which suggest that cellular plasticity might occur in the parahippocampal gyrus following early hippocampal damage (Villard et al., 2023). The population of immature neurons present in layer III of the entorhinal cortex and layer II of the perirhinal cortex have been shown to increase in number in monkeys with neonatal bilateral hippocampal lesions, while the number of mature neurons was shown to increase in layer III of the entorhinal cortex. Perhaps this increase in neuronal number in the entorhinal cortices (and elsewhere) promotes the contribution of non-hippocampal memory processes and spares some aspects of memory function. We hope future research, which make use of non-human animal models of DA, will give further insight into the compensatory processes that occur in the presence of early life brain injury.

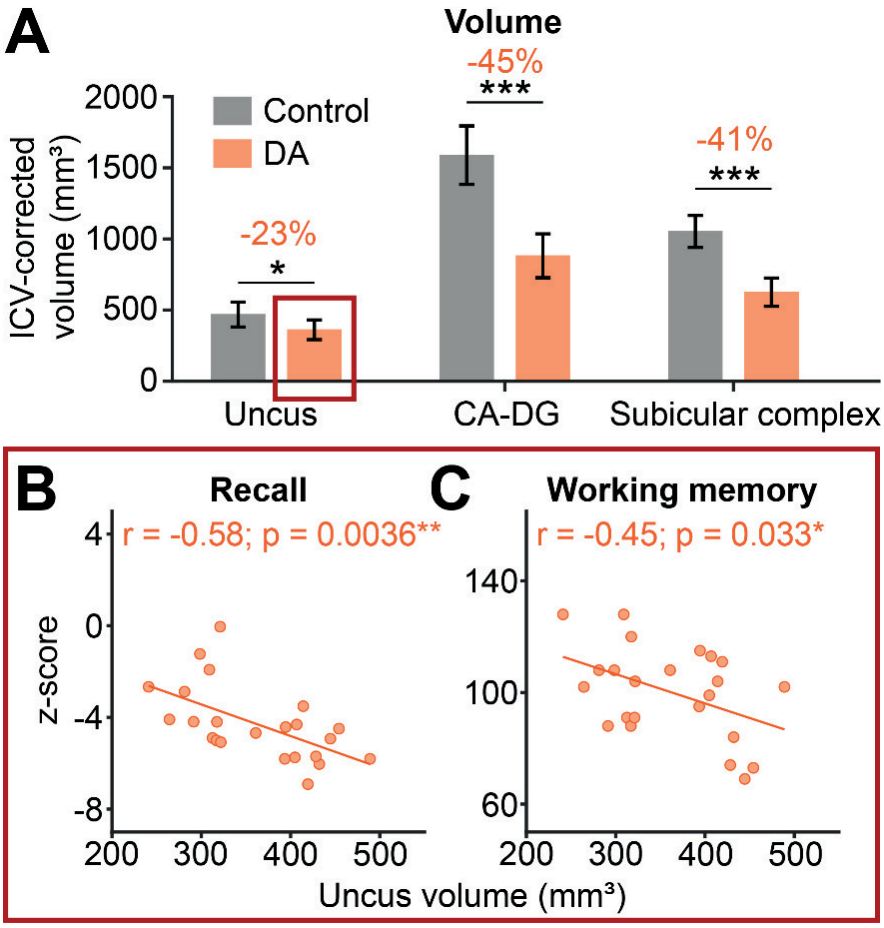


Figure S2.1. Volume of hippocampal regions and anatomo-functional correlations in DA. (modified from (L. J. Chareyron et al., 2023))

2.8.3 BOX 2: Prefrontal cortex and memory development

Maturation of memory processes results in increased localization of functions in core brain regions, such as the hippocampus and the prefrontal cortex (PFC) as well as of their interactions to enhance and stabilize performance as memory load increases (Ofen et al., 2007; Scherf et al., 2006). It is therefore critical to consider the PFC and its interactions with the hippocampus when tracing the emergent memory processes from infancy to their full maturation.

The PFC occupies the anterior pole of the mammalian brain and is involved in several cognitive processes, including working memory (WM) and rapid adaption

to various situations (Baddeley, 2012; Levy & Goldman-Rakic, 2000; Petrides, 2005). Age-related improvements in WM supported by the PFC have been documented from childhood to adolescence in humans, monkeys, and rodents (Cowan et al., 2006; Crone et al., 2006; Demaster & Ghetti, 2013; Druzin et al., 2000; Finn et al., 2010; Goldman-Rakic et al., 1983; Lipska et al., 2002; Lorsbach & Reimer, 2005; Luciana & Nelson, 1998; Ofen et al., 2007; Sander et al., 2012) and are believed to result from important anatomical, chemical and functional changes occurring in the PFC from infancy to adolescence (Goldman-Rakic, 1982, 1987; Huttenlocher, 1979; Huttenlocher et al., 1982a, 1982b; Kostovic, 1990; Tseng et al., 2007). Early in the postnatal period, overproduction of synaptic contacts and wiring occur, and synaptic density peaks relatively late (2–4 years of age in humans, 1-2 years in monkeys and after the fourth postnatal week in rodents)(Edin et al., 2007; Goldman-Rakic, 1982, 1987; Goldman-Rakic et al., 1983; Goldman & Alexander, 1977) and then refined as development advances until adolescence. Similarly, neuroimaging studies have indicated that gray matter (GM) volume increases across the cortex prior to puberty, reaching a peak around early to mid-pubertal period, followed by a post-pubertal decline during adolescence due to synaptic pruning (Giedd, 2004; Giedd et al., 1996; Gogtay et al., 2004; Thompson et al., 2005). Despite a lack of precise homologies between specific PFC areas in primates and rodents(Carlen, 2017), early investigation and genetic interventions in rodents have provided a deeper understanding of the PFC circuit wiring and its relationship to cognitive maturation (see (Chini & Hanganu-Opatz, 2021) for a review). Briefly, while the pruning of synaptic branches (Vanderhaeghen & Cheng, 2010) is modulated by molecular factors, electrical activity mainly controlled the refinement of connectivity with transient bouts of beta–low-gamma rhythmic oscillations generated by pyramidal neurons in the PFC supragranular layers (Bitzenhofer et al., 2017; Bitzenhofer et al., 2021; Bitzenhofer et al., 2020). These bouts of electrical activity occur naturally in response to incoming stimuli from the hippocampus (Ahlbeck et al., 2018; Brockmann et al., 2011) and appear to have important functional correlates (Bitzenhofer et al., 2017; Brockmann et al., 2011; Chini et al., 2020). In addition, modulation of excitatory and inhibitory neurons within the PFC supragranular layers leads to further development of intrinsic PFC circuitry. Indeed, excitation/inhibition (E/I) imbalance during early adolescence results in severe cognitive deficits (Bitzenhofer et al., 2021).

Importantly, evidence indicates that memory processes involve the participation of hippocampal-PFC interactions (Eichenbaum, 2017; Kirchhoff et al., 2000; Simons & Spiers, 2003). During spatial working memory, hippocampal synchronous activity has been shown to slightly precede the activity of PFC neurons in humans, monkeys

and rodents (Benchenane et al., 2011; Colgin, 2011; Gordon, 2011; Siapas et al., 2005; Wolf et al., 2009). During the early stages of postnatal development, the functional maturation of the PFC is driven by other cortical and subcortical regions, including the patterns of coordinated activity generated by the hippocampus (Bitzenhofer et al., 2020; Spencer-Smith & Anderson, 2009). Further, together with deficits in associative memory, early hippocampal insult yields WM impairment, which are not observed after hippocampal insult incurred in adulthood (rodents (Lipska et al., 2002; Tseng et al., 2007), monkeys (Heuer & Bachevalier, 2011, 2013), humans (Geva et al., 2016)). Concurrently, these WM deficits are associated with long range neural changes in the PFC, such as reduced number of interneurons and decreased spine density of pyramidal prefrontal neurons (Francois et al., 2009; Marquis et al., 2008), altered PFC firing patterns (O'Donnell et al., 2002; Tseng et al., 2007), decreased functional connectivity within the PFC cortical networks (Li et al., 2021) as well as anatomical connectivity between the hippocampus and PFC(Meng et al., 2016; Meng et al., 2014). Given that the critical role of hippocampal rhythmic activity in the early postnatal period for normal PFC maturation, it is tempting to suggest that as a result of the early hippocampal lesions, plastic changes within the PFC may have resulted from a lack of hippocampal inputs during postnatal period. Although the exact timing for the emergence of these plastic changes is still unknown, the above results stressed the importance to design future studies on the critical cross-talks between the hippocampus and PFC during development to provide a more precise neural account for the emergent memory processes from infancy through late adolescence.

2.8.4 BOX 3: Linking neuro- and episodic-like memory development

Links between neuro- and cognitive development remain relatively unclear. Drawing on the extensive literature described here, we will speculate on these links. We emphasise that the links we suggest are hypothetical and need to be tested experimentally.

As object ('what') encoding is known to develop first in mammalian W-W-W memory development, we speculate that this function may be supported by the early maturing subregions of the hippocampus, such as CA2, deep CA1 and distal CA3 as well as the perirhinal cortex which has been shown to be critical for object encoding early in life (Zeamer et al., 2015). Indeed, cells in these subregions may be preferentially innervated by the early maturing lateral entorhinal cortex (Bayer, 1980), which supports object encoding (Deshmukh & Knierim, 2011). In addition, we may speculate that, at least in the rodent, CA2 may play a particularly important role in object encoding, given its established role in olfactory memory in infant mice (Laham et al., 2021). As no

in vivo neural recording study has targeted these specific regions the neuronal representations that underlie the early emergence of this fundamental component of W-W-W memory remain to be elucidated.

In terms of 'what-where' (spatial and contextual) encoding, we hypothesise that the emergence of this ability depends on the maturation of place cells and the full tri-synaptic loop (i.e. ECII->DG->CA3->CA1). Rudimentary 'what-where' encoding, such as the ability to discriminate between different environments, may be possible before place cell representations become stable and are able to integrate multi-sensory cues and when hippocampal engrams are dense, such as has been observed during the third post-natal week in rodents (Langston et al., 2010b; A. I. Ramsaran et al., 2023; Wills et al., 2010). However, we conjecture that mature 'what-where' encoding, where animals can for example disambiguate environments whose sensory features overlap, depends on the availability of a precise spatial CA1 code and a sparse engram, which in the rodent is observed from the fourth post-natal week onwards (Langston et al., 2010b; A. I. Ramsaran et al., 2023; Wills et al., 2010).

Temporal ('what-when') encoding in W-W-W memory, we speculate may depend on the emergence of sequential encoding in CA1 (theta sequences and replay). Such sequential neuronal encoding has been found to develop relatively late, with the earliest inflection point found in 4th post-natal week in rodents (Muessig et al., 2019a). This agrees largely with the human literature on 'what-when' encoding which has also displayed a late inflection point (e.g. (H. Hayne & K. Imuta, 2011; Scarf et al., 2013)).

In terms of the neurobiological basis of memory retention, we speculate that this ability depends on the development of hippocampal reactivations and replay (which in turn depend on the maturation of SWRs). Reactivation of single locations have been reported in the third post-natal week in rodents (Muessig et al., 2019a). However, we reason that due to the immaturity of CA1 representations at this developmental stage, reactivations are not able to support long-term associative memory retention when they first emerge. Only when place cells start forming stable, specific and sequential functional representations do reactivations start supporting the retention of W-W-W memories. Further, we hypothesise that the development of memory retention may also depend on the maturation of hippocampal projections to the cortex. Hippocampal-cortical communication during reactivations is thought to play a critical role in the stabilization of new memories (Battaglia et al., 2004; Maingret et al., 2016). Studies have shown that the deep layers of the entorhinal cortex (ECV/VI) – the primary hippocampal cortical

output region - develop late (Jabes et al., 2011). As such, it may be that adult-like long-term retention only emerges once this extra-hippocampal communication pathway has developed.

2.8.5 BOX 4: Critical knowledge gaps

The development of memory retrieval process. The ontogeny of different retrieval processes (recognition, spontaneous/strategic recall) has not been studied systematically in any species. We encourage the non-human animal research community in particular to develop tests that tap into different retrieval process.

Temporal ('when') memory. Relatively little research attention has been devoted to this component of W-W-W memory, and much research thus far has focused on the sequential aspect of 'when' encoding (the order in which events unfold in an episode). However, recalling when an episodic memory occurred also involves making inferences based on contextual details (e.g. who one was with, what the weather was like, etc). We hope future research will pay particular attention to this inferential aspect of 'when' encoding and paradigms for studying temporal encoding in animals be developed further.

The development of core computational processes for memory. Namely, how does the gradual development of W-W-W memory and adult-like retrieval mechanisms relate to key mnemonic computational processes such as pattern completion and separation?

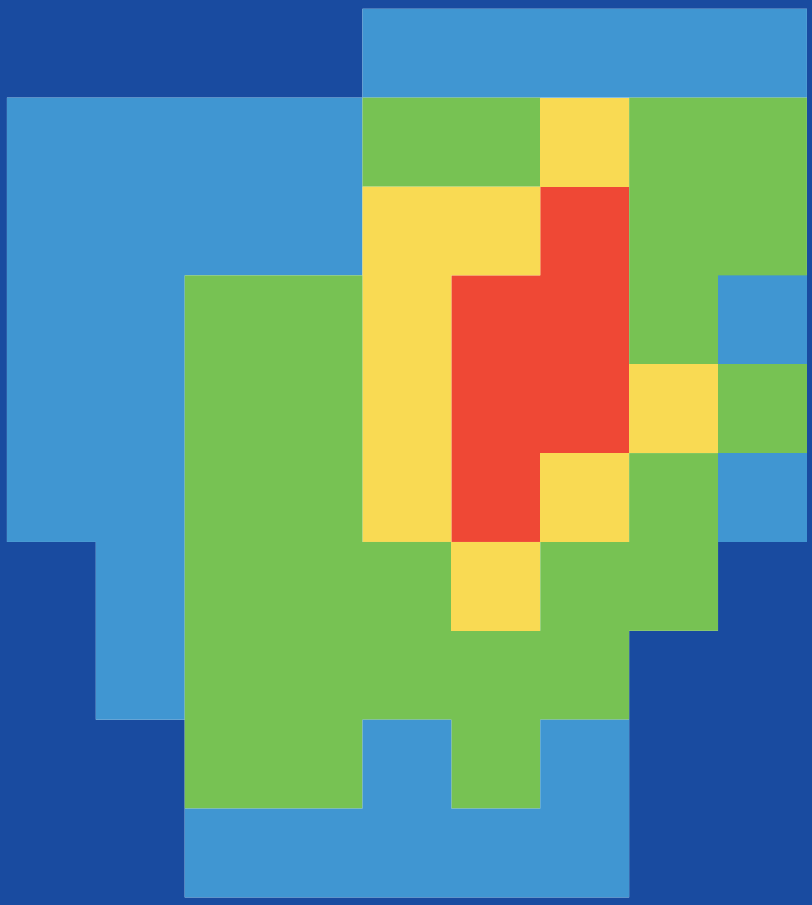
Relationship between neuro- and cognitive development. We do not know how the emergence of mature neuronal function (e.g. place cell, replay), relates to the development of W-W-W/episodic-like memory capability. Further, the relationship between structural development and memory development is largely unexplored.

The relationship between sleep and memory development. The contribution of sleep to learning is known to undergo development changes (Gomez & Edgin, 2016). It is of critical relevance to study how sleep contributes to episodic memory ontogeny.

Functional specialisation in development. A wealth of research has shown that the localisation of function in the developing brain is not the same as in the adult. Relatedly, other brain regions – such as the PFC - are implicated in core aspects of W-W-W/episodic memory. The role extra-hippocampal regions play in memory

development and changes to functional specialisation have hitherto received limited research attention.

Link between the development of executive function and episodic-like memory. The emergence of mature W-W-W/episodic memory – and particularly autonoetic/strategic recall - may not simply depend on the maturation of mnemonic processes but also executive function. We encourage the research community to explore the role of general cognitive abilities in memory development.



Chapter 3

Parallel maturation of rodent hippocampal memory and CA1 task representations

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Summary

Objective

Hippocampal-dependent memory is known to emerge late in ontogeny and its full development is protracted. Yet, the changes in hippocampal neuronal function that underlie this delayed and gradual maturation remain relatively unexplored. We sought to address the particular lack of studies directly relating neural and cognitive development.

Approach

We recorded ensembles of CA1 neurons while charting the development of hippocampal-dependent spatial working memory (WM) in rat pups (~2-4weeks of age).

Main results

We found a sharp transition in WM development, with age of inflection varying considerably between individual animals. In parallel with the sudden emergence of WM, hippocampal spatial representations became abruptly task specific, remapping between encoding and retrieval phases of the task. Further, we show how the development of task phase remapping could partly be explained by changes in place field size during this developmental period as well as the onset of precise temporal coordination of CA1 excitatory input.

Significance

This study is the first study directly relating neural development to the behavioural output of memory development. Our results suggest that a hallmark of hippocampal memory development may be the emergence of contextually specific CA1 representations driven by the maturation of CA1 micro-circuits.

3.1 Introduction

The hippocampus supports the ability to anchor memories for events in our lives to their spatial-temporal context (episodic memory (E. Tulving, 1972)). A capability central to adaptive decision-making and planning for the future. Yet, hippocampal-dependent memory is known to develop late – with the first two years in human life characterized by a near absence of episodic memory (Rubin, 2000) – and its full maturation is protracted (Ngo et al., 2018; Ramsaran et al., 2019). In recent years, scientists have begun elucidating the ontogeny of hippocampal neuronal representations in rodents (Langston et al., 2010a; Martin & Berthoz, 2002; Scott et al., 2011; Wills et al., 2010). These studies have shown that hippocampal place cells (O'Keefe & Dostrovsky, 1971) – the primary cellular model for hippocampal memory – can already be recorded early in third postnatal week (Langston et al., 2010a; Wills et al., 2010); before the first signs of hippocampal memory emerge (Akers et al., 2009; Green & Stanton, 1989b; A. I. Ramsaran et al., 2023). However, although present, various lines of evidence suggest place cell function during this period may still be relatively non-specific (Martin & Berthoz, 2002; Muessig et al., 2015, 2016; Scott et al., 2011). For example, developing place cells have been found to be less stable – they alter where they fire on multiple exposures to the same environment (Scott et al., 2011) and show less within-session stability (Langston et al., 2010a; Muessig et al., 2015; Wills et al., 2010) – and the accuracy of the spatial code increases with age (Muessig et al., 2015).

As well as providing a robust spatial signal, place cells are known to integrate non-spatial (contextual) information, such as upcoming trajectories and task-specific demands (a form of non-spatial encoding collectively termed 'splitter cell' activity) (Duvelle et al., 2023; Ferbinteanu & Shapiro, 2003; Frank et al., 2000; Griffin et al., 2007; Kinsky et al., 2020; Varga et al., 2024; Wood et al., 2000). The ability to integrate spatial as well as non-spatial information may be particularly relevant for the mnemonic functions that the hippocampus has been purported to support. Indeed, splitter cell activity has been found to predict choices on a spatial memory task (Pastalkova et al., 2008) and the strength of the splitter signal was found to correlate with working memory performance (Kinsky et al., 2020). As such, we sought to chart the ontogeny of this from of non-spatial hippocampal encoding.

To this end, we recorded from populations of CA1 place cells in P17-P28 rat pups – the developmental period when adult-like hippocampal memory emerges in rats (Akers et al., 2009; Campbell & Campbell, 1962; Green & Stanton, 1989b; A. I. Ramsaran et al., 2023) - while the pups carried out a hippocampal-dependent working memory task that requires animals to alternate between sample and

memory-guided task phases (discrete trial, delayed non-matching to place (DNMP) (Dudchenko et al., 2000; Shaw & Aggleton, 1993)). In adults, this task is associated with a strong influence of non-spatial features of the task on CA1 place cell activity – place cells display robust remapping between the two phases of the task (Griffin et al., 2007). Here we sought to chart the ontogeny of this form of non-spatial encoding, which we term task phase remapping, in relation to the maturation of hippocampal memory.

3.2 Results

Spatial WM emerges abruptly and can be individually modelled

We trained twenty rat pups to complete 20 trial pairs every day on the DNMP task (Figure 3.1A). Each trial pair started with a sample run, where access to one of the T-maze arms was blocked and the pups had to run to the end of the open arm to receive a food reward. Following a 15-sec delay, spent in an inter-trial box located behind the stem, a choice run began. In choice runs, the animals could enter either arm but were only rewarded if they chose the arm opposite the one they had run to on the preceding run. Upon the completion of a choice run, another sample-choice trial pair started (see Methods). To disentangle the effect of development from experience, we had animals start at different ages. Fourteen animals started in the pre-weaning period (P17-P18), while 6 animals started post weaning (>P21). Each animal was tested for ~1 week. Between P17 and P28 we observed a gradual improvement in the pups' average performance on the task ($r = 0.97$, $p < 0.0001$, $n = 9$ post-natal days, Figure 3.1B), reaching eventually performance comparable to adults ($t(16) = 0.49$, $p = 0.63$, 1-sample t-test comparing performance for animals tested on P24-P25 ($n = 17$ sessions) vs average adult performance). This is in agreement with previous work that showed pups can reliably carry out this task, and other hippocampal-dependent tasks, at around 3weeks of age (Green & Stanton, 1989a; A. I. Ramsaran et al., 2023; Travaglia et al., 2018). However, previous studies have also highlighted that the ability to carry out tasks similar to the DNMP emerges abruptly in individual animals (Douglas et al., 1973a). To address this question, we fitted sigmoid curves to the developmental curves of individual pups that started in the pre-weaning (<P21) period (Figure 3.1C, Figure S3.2, Methods). We found sigmoid fits captured the developmental curves significantly better than linear fits (AIC sigmoid fits = -37.98 (SD=6.88), linear fits = -34.26 (SD=6.27), paired-samples t-test: $t(12) = -2.78$, $p = 0.0017$, Figure S3.1C, $n = 13$ animals), suggesting the developmental emergence of this form of hippocampal memory occurs abruptly (i.e. overnight). Further, the timing of inflection points varied notably between animals (Figure 3.1C,D), with the earliest inflection point observed at P19 and the

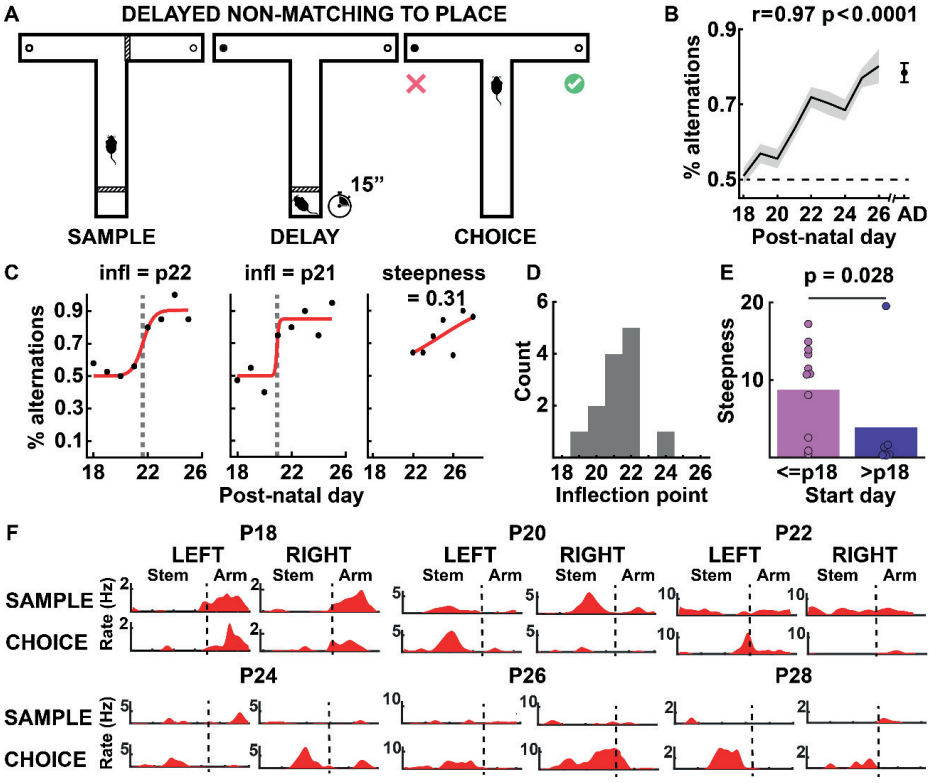

Figure 3.1. Hippocampal-dependent memory develops abruptly. **(A)** Schematic of the DNMP task. **(B)** Mean percentage of correct alternations across age. Shaded area shows SEM. **(C)** Fitted sigmoids to individual animal developmental curves (black circles show performance on individual days, red line the fitted sigmoid and the grey dashed line the inflection point). Far right plot shows sigmoid fit for animal that started post-weaning and the slope of the sigmoid. As the animal started post-weaning, the age of inflection is not shown. **(D)** Frequency distribution of age (PD) of inflection. **(E)** Sigmoid steepness for animals that started experiments on P18/P17 and those that started the experiment later. Circles show individual animal slopes. **(F)** Example linearized ratemaps from pups of different ages divided into the four different run types. Note, all four run-specific ratemaps, for a given post-natal day, come from the same cell.

latest at P24. Importantly, this abrupt improvement in performance could not simply be explained by experience, as animals that started experiments in the post-weaning period (n = 6) already performed above chance on day1 and showed a significantly shallower sigmoid fit (2-sample Kolmogorov-Smirnov test comparing sigmoid slope distributions between animals starting pre- vs. post-weaning, p = 0.028, Figure 3.1E, Figure S3.1A, Figure S3.2). Further, we did not observe a difference in development curves for pups who were weaned after experiments concluded as opposed to at P21 ($t(11) = 0.18$, $p = 0.86$, Figure S3.1B, 1-sample t-test comparing performance in weaning control sessions (n=12) to average performance post-inflection of all other animals) nor between female and male pups ($F(7,63) = 0.95$, $p = 0.47$, Figure S3.1D, repeated measures ANOVA, males n = 14, females n = 6). In tandem with these abrupt changes in performance, we also observed an increase in movement speed that correlated significantly with days to/from inflection (choice: $r = 0.66$, $p < 0.0001$; sample: $r= 0.60$, $p < 0.0001$, n = 75 sessions, Figure S3.3A-B). Further, as the ability to carry out the DNMP task emerged, pups spent proportionately less time near the start of the stem ($r = -0.37$, $p = 0.0013$, n = 75 sessions, Figure S3.3C) and more time on the arms ($r = 0.34$, $p = 0.0026$, Figure S3.3E). Time spent near the T-intersection did not vary linearly with days to/from inflection ($r = -0.038$, $p = 0.74$, Figure S3.3D).

Early place cells spatially remap, but encoding specificity emerges with spatial WM

Is this abrupt behavioural development supported by changes in neuronal activity? For 13 of the 20 animals tested we recorded in parallel from CA1 place cells (7-70 cells per session, mean = 17.11 (SD=9.02), Figure 3.1F, Figure S3.4, see Table 3.1 for an overview of the number of cells recorded per session). In the first instance, we assessed how CA1 spatial encoding changed during this developmental period and how, or if at all, it relates to the development of the animal's ability to carry out the task. To this end, we correlated ratemaps for the two arms of the T-maze (Figure 3.2A(i), Methods). Spatial correlations between ratemaps of the two arms were generally low (mean = 0.07 (SD=0.22), Figure 3.2A(ii), n = 75 sessions), suggesting place cells differentiated between the two geometrically identical arms. To ensure the low spatial correlations could not merely reflect unstable place coding, we correlated ratemaps for odd and even runs on the same arms (Methods) and compared the distribution of these stability scores against the left vs right arm remapping scores (Figure 3.2A(ii)). We found the remapping scores were significantly lower than the stability scores (mean = 0.30 (SD=0.15), $p < 0.0001$, 2-sample Kolmogorov-Smirnov test), indicating the low correlations between the left and right arm ratemaps indeed reflect remapping.

We next asked if spatial remapping changed in tandem with the developmental improvements observed for individual animals on the DNMP task. To this end, we correlated the average session spatial remapping scores against days to/from inflection (0 indicates first day after inflection, n = 75). Spatial correlations scores did not correlate with the development of DNMP memory ($r = -0.09$, $p = 0.47$, Figure 3.2A(iii)). Indeed, at the earliest ages tested CA1 cells showed reliable remapping between the two arms ($r = 0.052$ (SD=0.18), $t(5) = -3.05$, $p = 0.029$, 1-sample t-test comparing P17-P18 remapping (n = 6 sessions) vs stability), consistent with previous research (Muessig et al., 2016), and the remapping observed in the pups did not differ from adult spatial remapping ($r = 0.18$ (SD = 0.20), $t(86) = -1.44$, $p = 0.16$, 2-sample t-test comparing all pup (n = 75) and adult (n = 13) sessions).

As noted previously, studies in adult rodents have shown significant trajectory (left- vs right-bound paths, Figure 3.2B(i)) and task phase (sample vs choice trials, Figure 3.2C(i)) remapping in the DNMP task (Griffin et al., 2007). Next, we sought to chart their ontogeny. Starting with trajectory remapping, we found no evidence for this form of remapping in our data; the average correlation between right- and left-bound stem ratemaps did not differ from the stability distribution ($p = 0.23$, 2-sample Kolmogorov-Smirnov test, Figure 3.2B(ii)). Further, the degree of trajectory remapping did not show any relationship with the DNMP developmental curves ($r = -0.001$, $p = 0.99$, Figure 3.2B(iii), n = 75 sessions). On the other hand, we found the CA1 cells remapped strongly between the sample and choice trials ($p = 0.0014$, Figure 3.2C(ii)), and the degree of task-phase remapping correlated significantly with days to/from inflection point ($r = -0.5$, $p < 0.0001$, Figure 3.2C(iii), n = 75 sessions), becoming comparable to adult task phase remapping in the post-inflection period ($t(62) = 1.12$, $p = 0.27$, 2-sample t-test comparing task phase remapping during post-inflection sessions (n = 51) to task phase remapping of adult sessions (n = 13)). To note, we also correlated the different measures of remapping to post-natal age (Figure S3.5A-C). These correlations were notably weaker than those observed for inflection point (trajectory remapping: $r = -0.13$, $p = 0.25$; task phase remapping: $r = -0.22$, $p = 0.04$), highlighting the need to account for individual variation when studying the neuronal basis of cognitive development.

Importantly, the relationship between task-phase remapping and DNMP developmental curves could not be explained by experience. A partial correlation controlling for the effect of experience had only a small effect on the inflection point vs task-phase remapping correlation, and it remained robustly significant ($r = -0.47$, $p < 0.0001$). Indeed, using a general linear model to predict task-phase remapping

from experience, post-natal age and days to/from inflection (Methods) showed that only days to/from inflection could significantly predict developmental changes in task-phase remapping (GLM: inflection point: $t(71) = -4.56$, $p < 0.0001$; post-natal day: $t(71) = 0.94$, $p = 0.35$; experience: $t(71) = 1.2$, $p = 0.24$). Finally, we found movement speed did not differ between the two trial phases (choice = 21.24cm/sec (SD=10.87), sample = 19.01cm/sec (SD=10.88), $t(172) = 1.35$, $p = 0.18$), although median session speed increase significantly with age ($r = 0.52$, $p < 0.0001$). Importantly, task phase remapping remained a significant predictor of days to/from inflection after controlling for age-related changes in speed ($r = -0.38$, $p = 0.0011$).

To corroborate these findings and to explore where remapping occurred on the maze, we turned to a population vector analysis (Methods). For each spatial bin (4cm) we correlated the population vectors between sample and choice ratemaps for each session, and then computed the average correlation across all sessions recorded during the pre- and post-inflection period (pre-inflection n = 24, post-inflection n = 51). In agreement with the remapping analysis described above, we found population vector correlations were significantly lower during the post inflection period compared to the pre inflection period (Figure 3.2D, based on bootstrapping session population vectors 10,000 times). To note, dividing the post-inflection population vector correlations in two (peri: inflection points 0-2; post: >2 days post inflection) showed no further changes in remapping (all spatial bins $p > 0.05$, Figure S3.6). This suggests task phase remapping emerges abruptly in development, mirroring the abrupt development of hippocampal memory.

Next, we sought to characterize whether developmental changes in remapping reflect homogeneous changes in place cell task phase coding across the CA1 population. To this end, we fitted gaussian distributions to the pre- and post-inflection task phase remapping distributions (pre-inflection n = 516 cells PRE, post-inflection n = 702 cells, see Methods). During the pre-inflection period, we found that the task phase remapping distribution was best fitted with three Gaussian components (AIC = 432.35), and the three components were centred on $r = -0.05$ (66%), $r = 0.52$ (30%) and $r = 0.89$ (3.6%) correlation scores (Figure 3.2E). This suggests heterogeneous task phase encoding during the pre-inflection period, with some cells remapping while others did not. During the post-inflection period, however, the task phase correlation distribution could be captured by only two components (AIC = 230.97), one centred on $r = -0.13$ (30%) and another on $r = 0.20$ (70%, Figure 3.2E). Thus, the high correlation component ($r = 0.89$) observed during the pre-inflection period disappeared post inflection, and only two sub-populations – both centred on low correlation scores – were apparent in the

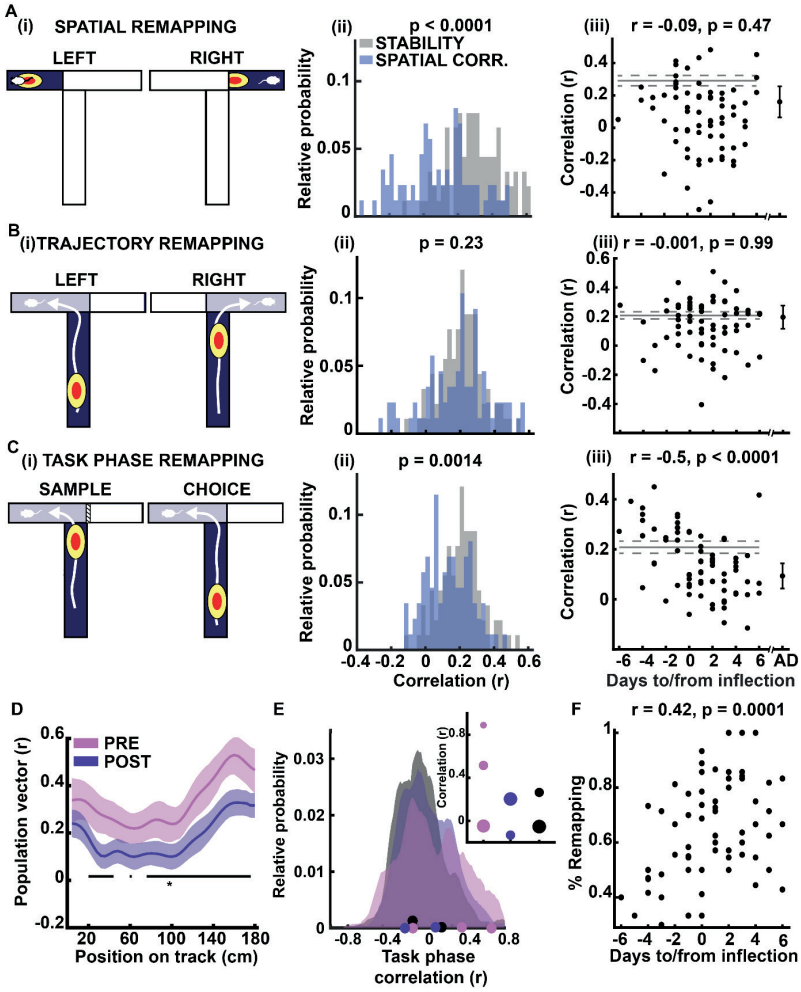

Figure 3.2. Task phase remapping ontogeny predicts maturation of hippocampal memory. **(A)** (i) Spatial remapping was computed by correlating place cell ratemaps for left and right arms. Dark blue areas of the maze indicate sections used to compute spatial correlations. (ii) Distribution of average session remapping scores (blue) and stability scores (grey). (iii) Mean session remapping scores as a function of days to/from inflection point. Horizontal grey line shows mean stability score along with standard deviation (dashed line). **(B,C)** Same as A but for trajectory and task phase remapping, respectively. Note, light blue areas in panel (i) are not included in correlation. **(D)** Population vector correlation between sample and choice ratemaps for pre (light purple) and post (dark purple) inflection periods. Shaded area shows 95% confidence intervals from bootstrapping data. Black line underneath PV indicates bins where there is a significant difference between pre and post inflection periods. **(E)** Distribution of task phase remapping scores for pre and post inflection periods as well as adults (grey). Circles on the x-axis show the centre of fitted gaussian components. Inset: Centre of gaussian components for pre and post inflection periods and for adults, y-axis shows the task phase ratemap correlation that corresponds to the centre of individual components. The size of the circle is proportional to the amount of data that is captured by individual components. **(F)** Proportion of cells remapping between choice and sample trials against days to/from inflection.

population, suggesting task phase remapping had become nearly ubiquitous. In agreement with this, we found days to/from inflection could be reliably predicted by the proportion of cells that showed task phase remapping in a session ($r = 0.42$, $p = 0.0001$, Figure 3.2F, $n = 75$ sessions). To note, fitting gaussian distributions to adult task phase remapping distributions ($n = 202$ cells, Figure 3.2E), also revealed two components (AIC = 47.75) centred on similarly low correlation coefficients of $r = -0.05$ (71%) and $r = 0.26$ (29%) as during post-inflection. This underscores the observations that task phase coding emerges abruptly in development.

These findings led us to ask what could explain the sudden developmental emergence of task phase remapping? We first explored whether days to/from inflection could be predicted by changes in place cell rate, place field size or place cell sparsity (Methods). Days to/from inflection showed no relationship to place cell activity rate in a session (peak rate: sample: $r = 0.19$, $p = 0.1$, choice $r = 0.09$, $p = 0.42$, Figure S3.7A, $n = 75$ sessions) nor to sparsity (% of cells active in a session: sample = $r = -0.21$, $p = 0.06$, choice: $r = 0.06$, $p = 0.62$, Figure S3.7B, $n = 75$ sessions). However, we observed a significant correlation between the size of place cell's place field and days to/from inflection (sample $r = -0.41$, $p = 0.0002$; choice $r = -0.23$, $p = 0.042$, Figure 3.3A-B, $n = 75$ sessions), suggesting spatial coding becomes more precise as cognitive development unfolds. To explore these findings further we investigated how firing rate variability within and outside a cell's place field changed in development (Methods). Although we found in-field rate variability did not correlate with days to/from inflection ($r = 0.10$, $p = 0.38$, Figure S3.7C, $n = 75$ sessions), variability outside the field became lower as the animal's developed the ability to carry out the task ($r = -0.26$, $p = 0.023$, Figure S3.7D, $n = 75$ sessions). Further, we found the ratio between out- vs. in-field variability to significantly decrease with days to/from inflection ($r = -0.28$, $p = 0.019$, Figure S3.7E, $n = 75$ sessions), suggesting out-field variability became relatively lower compared to in-field variability as the animal's developed, perhaps reflecting a reduction of firing outside a place cell's firing field. Consistent with this interpretation we found the in- vs. out-field firing rate ratio (higher ratio indicating higher relative rates inside vs outside the field) to increase with days to/from inflection ($r = 0.32$, $p = 0.0046$, Figure S3.7F, $n = 75$ sessions).

Developmental shift in the balance of CA1 inputs underlies functional specificity maturation

Alternatively, phase remapping may reflect maturation in the temporal coordination of input to CA1. CA1 receives primarily two glutamatergic inputs – one from layer three of the entorhinal cortex (ECIII) and another from area CA3. These two inputs are

thought to reflect distinct hippocampal network states, supporting complementary processes. ECIII input has been purported to support encoding-related processes while CA3 input may rather support memory-guided processes (Hasselmo et al., 2002; Manns et al., 2007). As the DNMP task requires animals to learn to alternate between encoding and memory-guided phases, perhaps the ontogenetic emergence of task-phase remapping, and thereby hippocampal memory maturation, reflects developmental changes in CA1 input alignment to distinct task phases. Namely, with development CA3 input may become more dominant and specific to the choice phase – which requires an execution of memory-guided actions - while ECIII input may be preferentially dominant during encoding-driven sample phases.

To address this question, we analysed CA1 single-unit activity and LFP markers that provide a proxy for CA3/ECIII input balance in CA1. In the first instance, we analysed theta phase preferences of place cell spikes during the sampling and choice phases. As ECIII input arrives closer to the peak of a theta cycle while CA3 input arrives near a theta cycle's trough (Douchamps et al., 2013; Fernández-Ruiz et al., 2017; Hasselmo et al., 2002; Lever et al., 2010; Mizuseki et al., 2009; Valero & de la Prida, 2018) (Figure 3.3C), we reasoned that during the post-inflection period sample phases should be associated with spikes occurring nearer the peak of theta-band oscillations relative to choice phase spikes, which may rather fall near the theta-band trough. For the pre-inflection period, on the other hand, we would expect no difference in phase preference for the two task phases. Consistent with this, we found place cells did not differ in their phase preference during the two task phases in pre-inflection period (sample mean angle = 131.5° (n = 120 cells), choice mean angle (n = 91 cells) = 110.4°, Figure 3.3D-E(i), $F(1,209) = 2.70$, $p = 0.10$, Watson-Williams test). During the post-inflection period, however, we found phase preferences between the two task phases differed reliably (sample = 111.4° (n = 99 cells), choice = 154.5° (n = 82 cells), $F(1,179) = 7.62$, $p = 0.0064$, Watson-Williams test, Figure 3.3D-E(ii)), with place cells firing nearer the peak of a theta cycle during sample phases of the task while spikes during choice phases tended to fall nearer the theta trough. Additionally, theta phase locking – which may reflect a shift in the balance between the two main inputs to CA1 (ECIII and CA3) (Guardamagna et al., 2022) – decreased significantly as the animals started to be able to perform the task reliably ($r = -0.67$, $p < 0.001$, n = 32 sessions, Figure 3.4A). Importantly, this effect was driven by the sampling trial phases ($p = 0.006$, pre-inflection n = 120 cells, post-inflection n = 99 cells, 2-sample Kolmogorov-Smirnov test, Figure 3.4B). Phase locking during choice trial phases did not change significantly between pre- and post-inflection periods ($p = 0.82$, pre-inflection n = 91 cells, post-inflection n = 82 cells, 2-sample Kolmogorov-Smirnov test, Figure 3.4C).

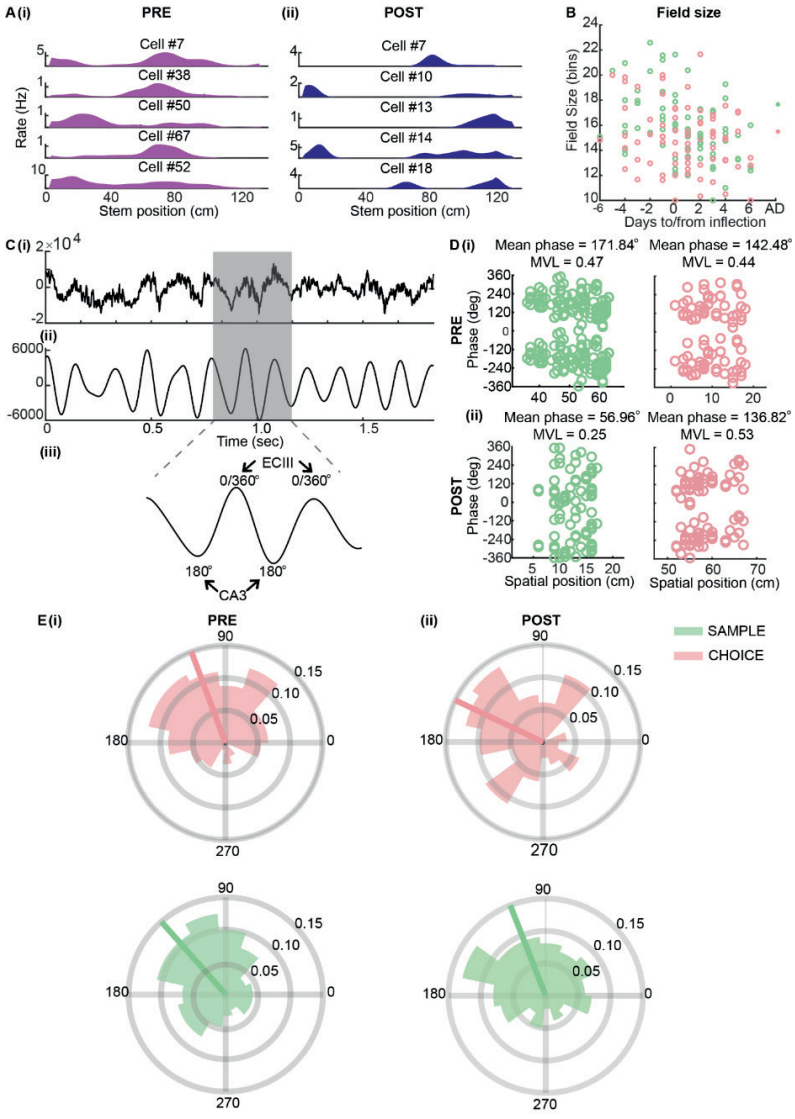

Figure 3.3. Hippocampal memory maturation is associated with an increase in hippocampal spatial specificity and task phase-specific theta-band firing preferences. (A) (i) Linearised ratemaps recorded in the pre (i) and post (ii) inflection period. **(B)** Average place field size for sample (green) and choice (pink) runs against days to/from inflection. **(C)** (i) Raw LFP trace from CA1 showing theta-band oscillations. (ii) LFP trace filtered in the theta-band (5-12Hz) showing the instantaneous amplitude and phase of theta-band oscillations. (iii) Enlarged version of two cycles of filtered LFP data showing the different timing of ECIII and CA3 inputs. **(D)** (i) Firing phase vs spatial location (within the place field) plot for two cells recorded pre-inflection (green/left = cell recorded during sample trials, pink/right = cell recorded during choice trials). Two theta cycles are shown for clarity. (ii) Same as (i) but for post-inflection data. **(E)** (i) Circular histogram of CA1 cell phase preferences for sample (bottom, green) and choice (top, pink) trials during the pre-inflection period. Coloured diagonal lines show the circular mean for each trial type. (ii) Same as (i) but for the post inflection period.

Finally, to corroborate these findings we investigated coupling of slow and medium gamma oscillations to CA1-recorded theta-band oscillations in sampling and choice trials and assessed how theta-gamma coupling changed between the pre- and post-inflection periods. Slow gamma (Figure 3.4D(i)), recorded in CA1, is known to derive from upstream CA3 activity while medium gamma (Figure 4D(ii)) oscillations are thought to originate from ECIII (Fernández-Ruiz et al., 2017; Guardamagna et al., 2022; Mizuseki et al., 2009). Thus, measuring the relative coupling of the two gamma-band oscillations to CA1 theta-band oscillations is another approach to assess the relative influence of ECIII and CA3 input over CA1 activity (Colgin, 2015; Guardamagna et al., 2022). As hippocampal gamma oscillations are known to increase in frequency in development (Rosa Cossart & Roustem Khazipov, 2022; Mohns & Blumberg, 2008), we calculated phase-amplitude coupling (PAC) between theta-band oscillations (5-12Hz) and oscillations of higher frequencies during sleep sessions (taking place after the DNMP task) in order to identify the boundaries of slow and medium gamma oscillations in our data (Figure S3.8A, Methods). Based on the session average PAC, we defined slow gamma as oscillations in the range of 18-30Hz and medium gamma as oscillations in the range of 40-70Hz. During the pre-inflection period (n = 24 sessions), we found the ratio between slow and medium gamma coupling to theta to be comparable during sample and choice phases of the task (sample slow/medium gamma ratio = 0.99 (SD=0.20), choice = 1.02 (SD=1.02), p = 0.48 based on 10,000 bootstrapped ratio scores, Figure 3.4E(i),F). During the post-inflection period (n = 51 sessions), however, we found a robust difference in the relative theta coupling of the two gamma bands between the two task phases (sample = 0.92 (SD=0.12), choice = 1.61 (SD=0.34), p = 0.0066 based on 10,000 bootstrapped ratio scores, Figure 3.4E(ii),F), with the ratio shifted towards medium gamma during sample phases but towards slow gamma during choice phases (Figure 3.4F). The same results were obtained when using slow and medium gamma frequency bands more frequently reported in the literature (slow gamma = 20-45Hz, medium gamma = 60-90Hz (Fernández-Ruiz et al., 2017), sample vs choice slow/medium gamma ratio pre-inflection: p = 0.45; sample vs choice slow/medium gamma ratio post- inflection: p = 0.014). To note, despite changes in movement speed between the two developmental epochs, these changes could not explain the shift in slow-to-medium gamma balance between the sampling and choice task phases (Figure S3.8B, Methods). In sum, consistent with the theta phase locking and phase preference analyses described above, it seems that the two excitatory inputs to CA1 become better aligned to the distinct task phases as the animals' hippocampal memory develops.

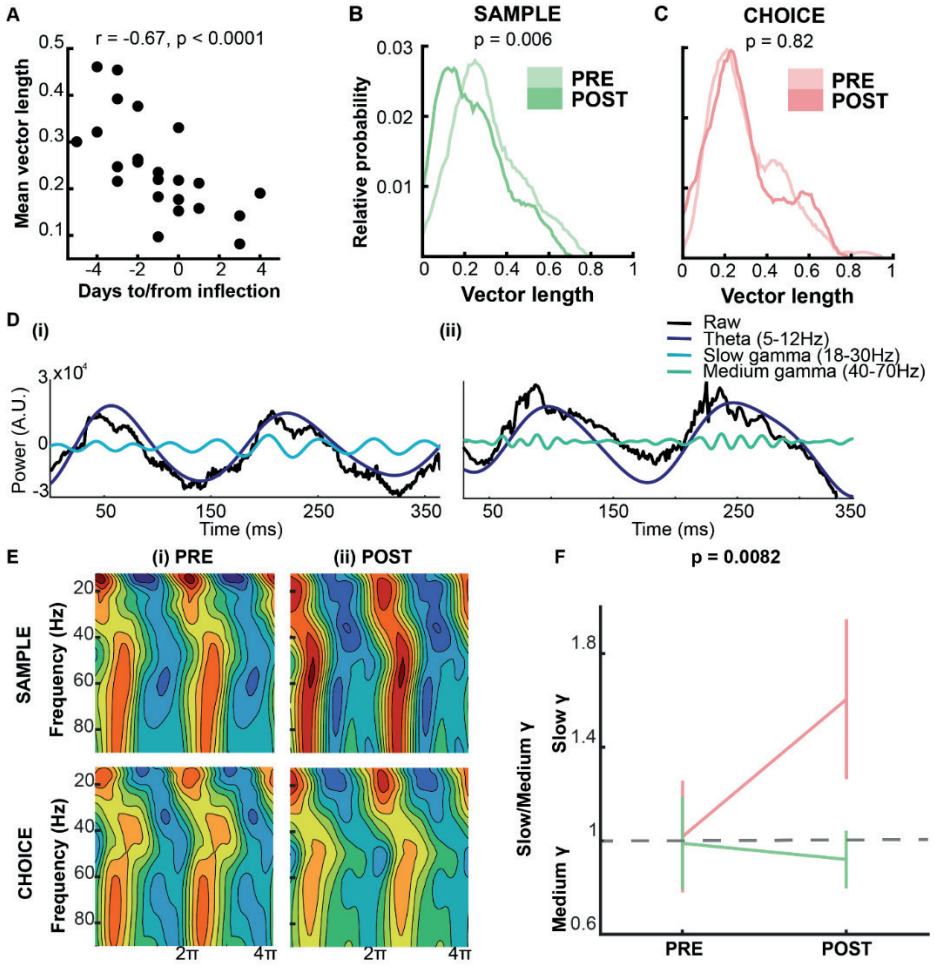

Figure 3.4. Hippocampal memory maturation is associated with the emergence of task-phase specific slow-to-medium gamma balance in CA1. (A) Mean session phase locking (Raleigh vector length) as a function of days to/from inflection. **(B)** Frequency distribution of phase locking scores for the pre and post inflection periods for sample trials. **(C)** Same as **(B)** but for choice trials. **(D)** (i) Black = raw LFP trace, purple = LFP trace filtered in the theta band (5-12Hz), blue = LFP trace filtered in the slow gamma (18-30Hz) band. (ii) Same as (i) but showing LFP trace filtered in the medium gamma (40-70Hz) band (green). **(E)** (i) Phase-amplitude coupling (average for all sessions) to theta-band oscillations during sample (top) and choice (bottom) trials, pre inflection, x-axis shows phase in a theta cycle. Note, two theta cycles are shown for clarity. (ii) same as (i) but for the post inflection period. **(F)** Average sample and choice slow/medium gamma coupling ratio for pre and post inflection periods, error bars show 1SD.

3.3. Discussion

Here, we show that hippocampal-dependent memory and CA1 task phase remapping – a form of hippocampal non-spatial coding - emerge in parallel in ontogeny. As the ability to carry out a spatial working memory matured, CA1 neuronal representations started to integrate spatial as well as non-spatial information – suggesting conjunctive spatial-non-spatial coding, a form of functional specificity, may underpin the emergence of mature hippocampal memory. In this respect, this study provides first-time insight into the neuronal coding changes underlying the switch from generic to specific memory content, which is considered an hallmark of memory maturation (Attila Keresztes et al., 2018).

What could be the origin of this neuro-developmental milestone? We propose it may reflect the combined emergence of precise CA1 place fields and adult-like temporal organization of CA1 glutamatergic input. On the one hand, as place fields become smaller and firing within the place field relative to firing outside the place field becomes more reliable, the ability to distinguish between overlapping spatial representations may increase. Alternatively, if with development the two phases of the task become associated with distinct excitatory inputs, this would naturally lead to different fields emerging for the two task phases. A more tempting hypothesis is that these phenomena are in fact inter-dependent: precise, information-rich, spatial representations might depend on effective integration of separate input streams in CA1, potentially relying on their temporal organization. The structured interaction of sensory- and memory-based information in CA1, derived from upstream ECIII and CA3 inputs, respectively, could be fostered by a shift from competing upstream inputs early in life to their spatio-temporal segregation in adults.

The maturation of input coordination may in turn be influenced by the development of key hippocampal and extra-hippocampal pathways. Synapses at distal CA1 dendrites (stratum lacunosum moleculare), which the direct ECIII temporo-ammonic pathway targets, emerge earlier in development than synapses at the more proximal CA1 dendrites (stratum radiatum) which are targeted by the CA3 Schaffer collaterals as a part of the tri-synaptic pathway (Durand et al., 1996; Tyzio et al., 1999). Moreover, the full maturation of CA3 may extend further into the post-natal period relative to the maturation of superficial EC (Jabes et al., 2011; Lavenex & Banta Lavenex, 2013). Thus, it could be that the maturation of CA1 input coordination may specifically depend on the development of the full tri-synaptic pathway. Mature CA3 input may be of particular relevance for the working memory task used here, as during choice phases the animals need to make a memory-guided decision, which may critically rely on adult-like CA3 input.

The medial prefrontal cortex (mPFC) may also play a role in the development of non-spatial coding. Namely, hippocampal-mPFC communication is known to be critical for spatial working memory tasks such as the one we used here (Jones & Wilson, 2005; O'Neill et al., 2013; Sigurdsson et al., 2010), and recent work showed that splitter cell activity in CA1 was impaired when a thalamic pathway (nucleus reuniens) connecting the mPFC to the hippocampus was severed (Ito et al., 2015). The mPFC is known to develop significantly during the post-natal period we studied (Bitzenhofer et al., 2020; Chini & Hanganu-Opatz, 2021; Pöpplau et al., 2024). Thus, the delayed development of task phase remapping, along with the emergence of temporally segregated inputs to CA1, could be influenced by the development of the mPFC and/or the development of mPFC-hippocampal pathways. Hopefully, future studies will elucidate the establishment of different hippocampal pathways and how their development relates to the emergence of mature hippocampal memory and neuronal coding.

Lastly, in our study we did not observe robust trajectory coding – place cell activity on the stem of the T-maze did not differentiate between left- and right-bound paths. What could this mean for the development of this form of hippocampal non-spatial coding? It could be that trajectory coding develops after task phase coding and, thus, we did not capture its ontogeny. However, even in the adults tested, we found trajectory remapping to be numerically weaker than task phase remapping (see Figure 3.2B(iii)-C(iii)). This is consistent with other adult studies using the same task (Griffin et al., 2007), suggesting perhaps the structure of the DNMP task determines which form of non-spatial coding place cells express. Furthermore, trajectory coding is known to increase with experience (e.g. Levy et al. (2021)). In our study, animals, irrespective of age, were not tested for extensive periods (up to 1 week). Potentially, with more extended recordings we would have observed trajectory coding. We hope prospective studies that use alternative spatial alternation paradigms (e.g. continues/delayed alternation where task phase is consistent throughout) and where testing occurs over longer periods of time, can shed light on this important question.

To conclude, here we show that the abrupt maturation of hippocampal-dependent memory occurs in parallel with the ontogeny of conjunctive spatial-non-spatial coding in CA1 place cells. The ontogeny of this form of encoding specificity in CA1 cells took place in tandem with the emergence of spatial-temporal segregation of CA1 excitatory inputs. Together, these findings provide unprecedented insight into the neurodevelopmental milestones that underlie the emergence of hippocampal memory and offer novel support for influential theories that propose non-spatial

coding is critical for hippocampal mnemonic capabilities (Ainge et al., 2008; Hasselmo & Eichenbaum, 2005) and models suggesting distinct hippocampal micro-circuits support complementary components of hippocampal memory (Colgin, 2016; Hasselmo et al., 2002; Valero & de la Prida, 2018).

3.4 Methods

Experimental model and subject details

Twenty Lister Hooded rat pups were tested on the DNMP task of which thirteen Lister Hooded rat pups (30-52g at implantation) underwent a surgical procedure to implant a microdrive carrying eight or sixteen tetrodes of twisted 17 µm HM-L coated 90% platinum, 10% iridium wire (California Fine Wire), targeting the right CA1 (ML: 2.0-2.3mm, AP: 3.0mm posterior to bregma). Electrode tips were gold plated to reduce impedance to 150-300kOhm at 1kHz. Pups were allowed to recover from surgery housed together with littermates (and dam if pre-weaning) for 48h. The animals always had *ad libitum* access to water and food, and were housed on a reversed 12-h light-dark cycle. Eleven adult Lister Hooded rats (330-400g at implantation) underwent the same procedure as pups. Adult procedures differed from pup procedures in CA1 target coordinates (ML: 2.0-2.3mm, AP: 3.8mm posterior to bregma), one week of post-operative recovery, and they were housed individually.

Electrophysiological recording

After the post-operative recovery period, electrophysiological activity was screened two to three times a day. All recordings were performed using an Axona recording system (Axona Ltd., St. Albans, UK) which recorded spike-threshold triggered single unit activity, continuous LFP, and position data. Each channel was amplified 5000 – 15000 times and recorded referenced to another channel on a separate tetrode. Spikes and LFP were sampled at 48KHz. Animal position was determined using an overhead infrared (IR) camera recording the location of an array of IR light-emitting diodes (LED) mounted on the headstage. Tetrodes were gradually advanced ventrally in 62.5 – 125µm steps, at least 3h apart, until place cells and sharp-wave ripples were detected.

Experimental apparatus and procedures

All experiments were performed in a dark room with no natural sources of light. The experimental area of the maze was surrounded by thick opaque black curtains on all sides. The experimental arena consists of a dark brown wooden digit-8 maze (140x140cm) with textured wood running surface. A T-shaped portion of the maze

was used for the DNMP task, the remaining parts of the maze were blocked off using black metal barriers. A black plastic food well holding 0.1ml of liquid was placed at the end of each arm of the T-maze. In between trials the animals were placed in a Delay box (12x12cm) at the start of the stem of the T-maze. Access to the stem was blocked off with a tall removeable barrier. Sleep recordings were conducted in a tall round opaque black plastic box (25x48cm), filled with bedding sand, that was placed on top of the centre of the stem of the maze, directly underneath the IR camera. These sleep sessions were used to define LFP bands for gamma oscillations.

Two days prior to experiments, animals were habituated for a single 10–15-minute session per day. Habituation was carried out on the tracks of the digit-8 maze that were unused in the T-maze, such that the physical characteristics of the tracks are identical to the T-maze tracks, but no part of tracks overlapped between habituation and T-maze. During habituation, animals were allowed to self-initiate walking between two ends of a linear track with food wells filled with soy milk at each end. The experimenter refilled the food wells with milk as necessary.

The task was performed in two identical sessions per day, at least 3 hours apart during which time the animals rested in the homecage. The animals were not food nor water deprived, and the conditioning reward was 0.1ml of soy milk formula. Each trial-pair consisted of two runs – Sample and Choice. Each Sample trial had access to one of the arms blocked off with a removable barrier, and food was placed in the open arm. The selection of left/right open arms during Sample trials was pseudo-randomised. When the animal reached the end of the open arm and drank its food reward it placed in the Delay box for 15 seconds. The Choice trial started after the Delay door was lifted for the animal to walk out into the stem. In this run, both arms were open. The pup got rewarded if they chose the arm opposite to the one rewarded during the Sample trial. After each trial-pair, the animal was placed into an inter-trial interval (ITI) box outside the maze for 30-45s intra-trial interval.. In a given session the animal completed 10 sample-choice trial pairs and each sessions lasted between 15-45 minutes. Thus, in a day an animal completed 20 sample-choice trial pairs. Immediately after finishing each session the animals were placed into the sleep box and allowed to rest for an hour.

Data inclusion/exclusion

20 animals were trained on the DNMP task, from 13 of these animals we collected CA1 single unit and LFP data in parallel with the behaviour data. Of these 13 animals, 11 were included in the inflection point analyses where sessions determine the sample size (e.g. Figure 3.2A-C,F, Figure 3.3A-B, Figure 3.4D-F)). The

two left out animals were excluded as for one of them we only obtained behavioural data for 4 days (insufficient to get a reliable sigmoid fit) and for the other one the sigmoid fit had an insufficiently steep slope (threshold = 0.4). To note, we started testing the latter animal in the post-weaning period (from P22). Importantly, all 13 animals from which we recorded single neuronal activity were included in analyses where cells were the basis for sample size (e.g. Figure 3.2D-E, Figure 3.3C-E, Figure 3.4A-C) as these analyses simply divided the data into pre and post inflection periods. We allocated the two animals for which we did not have an inflection point to a developmental period based on the ages that we had data from in each of them (e.g. for one animal we only recorded on P18 and P19 so this data was submitted to the pre inflection group and for the other animal we recorded from P24 onwards and as such this data was submitted to the post inflection group).

For a session to qualify for inclusion, we had to record at least 5 place cells in the session (based on shuffling Skaggs Information scores). This resulted in 87 sessions, of which for 75 we had an inflection point calculated. Further, for phase preference and phase locking analyses (see Figure 3.3C-E and Figure 3.4B,C) a cell was included only if it emitted at least 10 spikes within the place field, this resulted in the inclusion of 392 cells for these analyses. For session average phase locking analysis (Figure 3.4A), we only included sessions where we had least 5 cells that survived the spike number threshold. This resulted in the inclusion of 32 sessions.

Inflection point analysis

To determine developmental inflection points on the DNMP task for individual animals, we fitted sigmoid curves to individual animals' daily performance data. Specifically, we fit a sigmoid curve to the data using the standard logistic function (Equation 1) where *d* denotes the chance level performance which is set to 0.5, *a* represents the animal's highest daily performance mean, *c* is the steepness of the curve ranging from 0 to 20, and *b* the inflection point of the sigmoid constrained between the animal's first and last post-natal day. We used the nonlinear least squares fit option in Matlab R2019b (Mathworks, MA) in order to fit the model to the data. Any animal with fewer than 5 daily means (n = 1 animal) or best fit slope below 0.4 (N=1) were excluded from the inflection point analyses.

In cases where the inflection point given by the fitted model falls between two whole numbers, we always rounded up the value. Therefore, the next PD after the inflection point is determined to be day 0. For Pre vs Post analyses, we divided the data into sessions prior to the inflection point (Pre), and sessions from day 0 onwards (Post). For the analysis reported in Figure S3.4 where we further divided

the Post period, Peri was defined as the data from day 0 to day 2, and Post as data form day 3 onwards.

$$f(x) = d + \frac{a}{1 + e^{-c(x-b)}}$$

To compare linear and sigmoid fits we computed the Akaike information criterion (AIC) for linear and sigmoid fits and compared them using a paired samples t-test. To compare steepness of fitted sigmoids between animals who started experiments in the pre-weaning period vs those who started in the post-weaning period we used a Kolmogorov-Smirnov test.

Analysis of spatial behaviour

To analyse changes in spatial behaviour during the DNMP task in development we first analysed the average running speed in a session, excluding any periods where the animals' movement speed was below 3cm/sec. We analysed running speed separately for sample and choice trials to capture any differences in developmental trends for the two task phases. The session averages were then correlated (using a Pearson correlation) with days to/from inflection.

Further, we investigated if spatial exploratory behaviour on the T-maze changed during this developmental period. For this purpose, we divided the maze into 3 equally sized physical sections (each 70 cm long). The first section spanned the start of the stem until the middle of the stem ('start'). The second section started from the middle of the stem and ended at the T-junction ('approach'), the last section spanned the length of either the left or right arm ('end'). For each section we summed the total dwell time in a session and divided this number by the duration of the session. The proportion of time spent in individual sections were then correlated with days to/from inflection using a Pearson correlation.

Effect of day of weaning and sex on hippocampal memory development

To determine if day of weaning influenced the development of hippocampal memory, we compared the daily performance of animals who were weaned at P28, and for whom testing started at P23, to the average performance of other animals (weaned at P21) during the post-inflection period using a 1-sample t-test. To assess if the development of hippocampal memory differs between male and female rats, we carried out a repeated measures ANOVA where performance across days for individual animals was the within-subject factor and sex the between-subject factor.

Place cell analysis

All analyses were restricted to putative principal cells, identified by manual inspection of waveforms across the entire recording session. KlustaKwik was applied to spike-thresholded data to sort the data into clusters and then the clusters were manually curated in Tint (Axona Ltd.). We classified spike sorted neurons as place cells by computing Skaggs Information (bits per second) for run-type separated spikes (Skaggs Information was computed separately for choice left, choice right, sample left and sample right runs). The Skaggs Information value we obtained we compared against a null distribution generated by random permutations of spike times. Cells that exceeded 95th percentile of their own shuffle were deemed place cells. Sessions containing fewer than five cells with significant Skaggs information values were excluded from further analyses.

To generate ratemaps, spike data was divided into the four different trial types (e.g. Sample left, Choice left, etc). Spikes that occurred during stationary periods (<3cm/s) or when the animal was located near the start of the stem (<10cm) were excluded. Next, we linearised animals' paths, binned dwell time and total number of spikes in 2cm bins, computed firing rates by dividing the binned spikes over binned dwell time, and smoothed them using a Gaussian kernel (sigma= 3 bins).

Remapping analysis

To analyse remapping between the different trial types we correlated the spatial ratemaps for pairs of runs using the Pearson correlation coefficient (empty bins in both ratemaps were removed). Spatial remapping was performed only on the bins corresponding to the arms of the T-maze. The rest of remapping analyses excluded the arms and were only performed on the bins corresponding to the central stem of the T-maze, which is the only section of the track common to all four run types. Correlations between left- and right-bound ratemaps were refer to as trajectory remapping, while correlations between Sample and Choice ratemaps we term task phase remapping. To ensure remapping scores did not just reflect unstable spatial firing, we compared the remapping scores to correlations scores obtained by correlating the ratemaps for odd and even runs for a given trial type. To assess if a particular type of remapping was present in the population we compared the distribution of mean session remapping scores to the stability scores using a 2-sample Kolmogorov-Smirnov test.

To assess if remapping changed with development, we correlated average remapping scores obtained in a session with post-natal age/inflection point using a Pearson correlation coefficient. To rule out the effect of experience and

changes in median speed during development, we used a partial correlation where the relationship between inflection point and remapping was computed while controlling for the effect of experience/median speed. To compare the relative influence of inflection point, post-natal age and experience we used a General Linear Model (GLM) with remapping scores as the response variable and inflection point, post-natal age and experience as the predictors.

To assess if the proportion of cells remapping between task phases in a session correlated with inflection point, we calculated the proportion of cells with task phase remapping scores above r = 0.25 and correlated these session proportions with inflection point.

Population Vector Correlation Analysis

To examine the distribution of task phase remapping remapping across the track, we correlated the population vectors for choice and sample trials. Specifically, for each spatial bin (4cm) we computed the Pearson correlation coefficient for z-scored activity of all cells active in a session. The first 10cm at the start of the stem were removed to exclude areas of the maze associated with immobility. The average population vector was then computed for PRE and POST inflection periods and 95% confidence intervals (CIs) computed to assess which spatial bins differed significantly between the two periods. The average Pre and Post population vector correlation was then smoothed with a Gaussian kernel (sigma = 8cm). To compute the CIs we bootstrapped the session population vector correlations 10,000 times, repeating the analysis separately for Pre and Post inflection periods, for each iteration of the bootstrap we computed the mean population vector correlation. From the bootstrapped data we obtained the 2.5^{th} and 97.th percentile for each inflection period, if the CIs for the two periods did not overlap we deemed the comparison significant. The same procedure was used to compared the population vector correlations between the period immediately after inflection (inflection points 0-2, Peri) and the subsequent days.

Fitting gaussian components

To fit gaussian components to the distribution of task phase remapping scores during the PRE and POST inflection periods we used the Matlab function fitgmdist, we fitted 1 and 4 components and used the Akaike Information Criterion (AIC) to determine the model with the best fit.

Place field analyses

Field size and peak rate were assessed by first using the region props function in Matlab on rate thresholded ratemaps (bins > 50% of the peak rate of the ratemap). Small fields detected with this method (<20cm long) were removed. Then the area of the field was used as a measure of field size and the highest rate within the field a measure of peak rate. If a cell had multiple fields the average size and peak was computed. To measure sparsity, we computed the proportion of all cells recorded there were had a significant Skaggs information value in all four run types.

To investigate changes in firing rate variability within and outside a place cell's place field in development we constructed ratemaps for individual runs of a given trial type (e.g. sample left). We then computed the standard deviation of all the individual run ratemaps which resulted in a vector showing the standard deviation in rate for every bin on the track. This vector was then divided by the session ratemap for that trial type (to control for changes in firing rate in development). We then computed the average standard deviation for bins inside and outside the field, we term these variables a cells in- and out-field variability, respectively. To compute the ratio between in- and out-field variability, we divided the latter by the former. On this measure, a number below 0 suggests variability is lower outside the place field compared to inside the field.

To investigate how firing rate within a field changed in relation to rate outside the field in development we computed the average rate within a place field for a given cell and divided this number by the average firing rate outside the place field. On this measure, a value above 1 indicates firing rate is higher inside the place field compared to outside the place field.

To assess how these place cell features changed with development we correlated them against post-natal age/inflection point using the Pearson correlation coefficient. To control for the effect of field size we used a partial correlation, where inflection point and task phase remapping were the predictor and response variables, respectively, and field size the covariate.

Theta phase analyses

To analyse theta phase preference and phase locking to theta-band oscillations during Sample and Choice trials we first identified the electrode in the CA1 region with the highest power in the theta band (5-12Hz) using LFP data downsampled to 1.2kHz. We performed a wavelet transform to extract the instantaneous phase of the channel's signal in the theta band (Morelet wavelet with 7 cycles). We then used

the extracted phase to identify the theta phase of each spike. We filtered out low theta periods where the power of theta was below the mean. Further, we excluded stationary period (<3cm/sec) and only analysed the phase for cells who still had at least 10 spikes within their place field for given run after this filtering.

To compute the phase preference of each cells during sample and choice runs we calculated the circular mean for each trial type. To assess phase locking we computed the Resultant Vector Length for each cell's phases. To compare phase preference between sample and choice runs for the two inflection periods we used the Watson-Williams test which compares circular means and assumes an underlying Von-Mises distribution. For phase locking data, we first assessed if phase locking changed with inflection point. To this end, we used a Pearson correlation coefficient between the session mean phase locking scores (for all trial types) and days to/from inflection (sample size is based on number of sessions for this test). We then divided the phase locking scores for individual cells into sample and choice groups and compared the distribution of phase locking scores for each task phase during pre and post inflection periods, using a 2-sample Kolmogorov-Smirnov test (where sample size is derived from the number of cells).

Theta-Gamma Coupling

To measure coupling of slow and medium gamma oscillations to theta-band oscillations, we filtered the LFP data recorded in DNMP and sleep sessions so to include only samples where theta power was above the mean. For DNMP session data, we separated the data into sample and choice task phases. We then computed the phase-amplitude coupling between theta phase and amplitude of oscillatory components between 15 and 200 Hz: we first extracted the phase of the oscillatory component in the theta band (5-12 Hz). Then we binned theta cycles into 26 phase bins and for each phase bin we computed the average power of the oscillatory components at higher frequencies (>15Hz) obtained from a wavelet decomposition of the full signal. Thus, for each session we obtained a phase-amplitude 2-D matrix of coupling strengths where each value corresponds to a particular combination of theta phase interval and degree of amplitude modulation of a faster oscillation. These couplings were then z-scored across each frequency band and a mean phase-amplitude coupling matrix computed by taking the average of all sessions (for DNMP data the average was computed for pre-sample, pre-post, pre-choice and pre-post periods separately).

As gamma-band oscillations are known to increase in frequency in development (Rosa Cossart & Roustem Khazipov, 2022), we used the average 2-D matrix for sleep

sessions to identify the boundaries of gamma-band oscillations. The matrix for the pup sessions showed a clear amplitude modulation in the 18-30Hz frequency range; hence, we termed this band 'slow gamma'. The matrix for the pup sessions, on the other hand, did not show a clearly separated component at higher frequencies. For this reason, we turned to the adult phase-amplitude coupling matrix to identify a medium gamma band. Here, a prominent component was observed between ~50-60Hz. Given developmental changes in oscillatory frequency, we decided to define the medium gamma band broadly around this component (i.e. from 40-70Hz). Importantly, to ensure our results were not influenced by these specific definitions, we replicated the theta-gamma coupling analysis using different frequency bands (slow gamma = 20-45Hz, medium gamma = 60-90Hz) which are more representative of the bands commonly reported in the (adult) literature (Guardamagna et al., 2022).

To assess the ratio between slow and medium gamma coupling to theta, we identified the highest coupling observed in the average choice and sample phase-amplitude coupling matrices for the two gamma bands, and divided the coupling observed in the slow gamma band by the coupling observed in medium band. Here a value above 1 indicates strongest coupling to slow gamma compared to medium gamma. To assess if slow-to-medium gamma coupling to theta-band oscillations differed between sample and choice trials during the two inflection periods, we bootstrapped the session phase-amplitude coupling matrices 10,000 times, and for each iteration of the bootstrap we computed the average phase-amplitude coupling matrix for each task phase, the ratio of slow-to-medium gamma coupling for a given task phase and the difference in slow-to-medium gamma ratios between the two task phases. We then computed 95% confidence intervals for the difference score distribution to assess if the balance in slow-to-medium gamma coupling to theta differed significantly between choice and sample trials.

To control for the effect of speed during different inflection periods, we repeated the analysis above for different speed bands (low: 3-20cm/s, mid: 20-40cm/s, high: >40cm/s), we then assessed if the difference in slow-to-medium gamma ratios during each inflection period for individual speed bands differed significantly from the original data. To this end, we computed the difference between bootstrapped slow-to-medium gamma ratios during individual inflection periods as described above.

3.5 Acknowledgments

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H.F.Ó. conceived of the original experiment. J.B. collected the original data. J.B., F.S., and H.F.Ó. conceived, designed, and performed the analyses. J.B., F.S., and H.F.Ó. wrote the manuscript.

3.6 Supplementary materials

Animal	Session	Day to/from inflection point												
		-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6
09B1	1						6	7	7	8	15	8		
09B1	2								10	7	11	9		
09B2	1						10	19	11	15	19	22	16	7
09B2	2						10	16	15	15	18	21	11	
11B2	1								7	11	6	7	6	6
11B2	2								16	7	7	12	7	6
13B1	1				20	27	15	10	7	12	7			
13B1	2					18	10		8	12	8			
13B2	1	10	15	15										
13B2	2		20	31										
14B1	1						10	9						
14B1	2													
14B2	1					16	20	17	16	11	6			
14B2	2						24	15	16	8				
21B1	1			15										
21B1	2													
21B2	1				11									
21B2	2				7									
23B1	1			17										
23B1	2			13										
Total		10	35	91	38	61	105	93	113	106	97	79	40	19

Table 3.1. Place cell yield per session (related to Figure 3.1). Numbers in each cell indicate how many place cells were recorded per session for each day (note, days indicates as days to/from the inflection point). Note, two more animals were included (14B3 and 25B1), but as they did not have an inflection point calculated they are not included here. For reference, these animals add a total of 12 more session with a total of 338 cells (range: 14-70 cells per session).

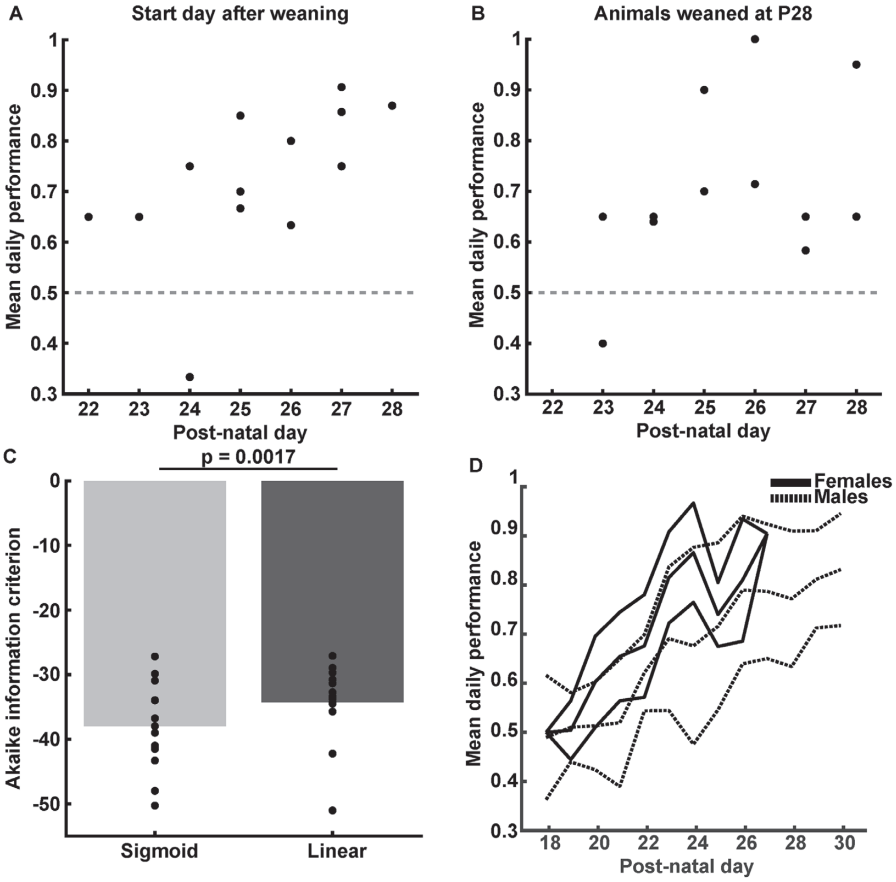


Figure S3.1. Spatial working memory develops abruptly and maturation is not affected by experience of day of weaning. (A) Daily performance of animals that started experiments after weaning (P21). **(B)** Daily performance of pups that were weaned after experiments concluded. **(C)** Sigmoid (left) and linear (right) goodness-of-fit values for individual DNMP developmental curves. **(D)** Mean performance of female and male pups across age (PD). Error bars show 1SD.

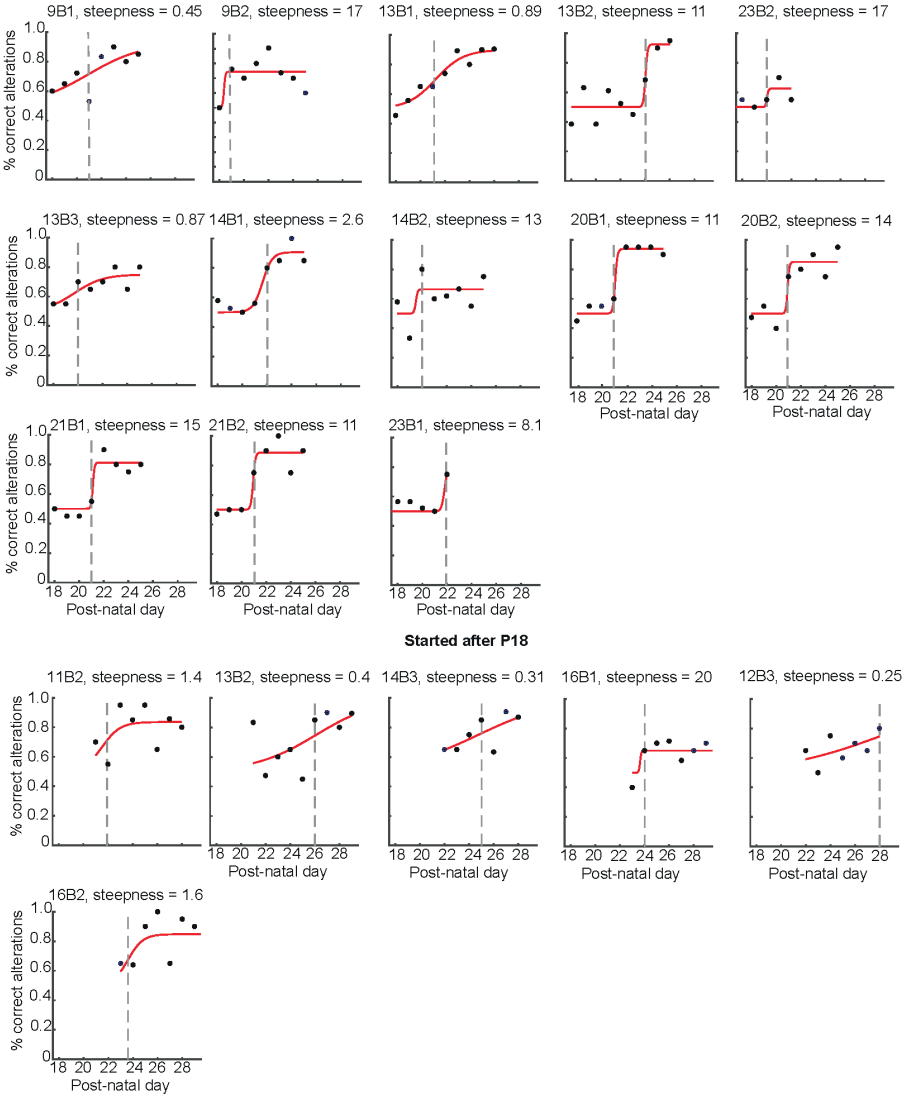


Figure S3.2. Developmental curves for individual animals with sigmoid fits. Related to Figure 3.1. Top: Daily performance (black circles) for all pups who started in the pre-weaning period. Red line shows fitted sigmoid and the title the animal ID slope of the sigmoid. Bottom: same as top, but for animals who started in the post-weaning period.

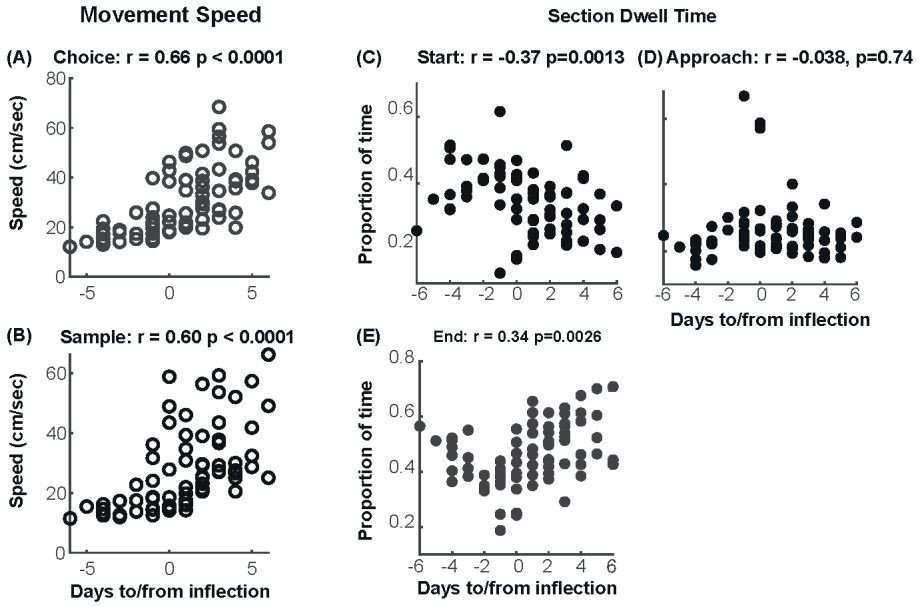


Figure S3.3. Development of hippocampal memory is associated with increased locomotory speed and changes in spatial exploration. Related to Figure 3.1. (A) Session movement speed (cm/sec) during choice trials plotted against days to/from inflection. **(B)** Same as **(A)** but for sample trials. **(C)** Proportion of time spent near the start of the stem plotted against days to/from inflection. **(D-E)** Same as **(C)** but for the approach (section near the T-junction) and ends (arms of T) of the T-maze.

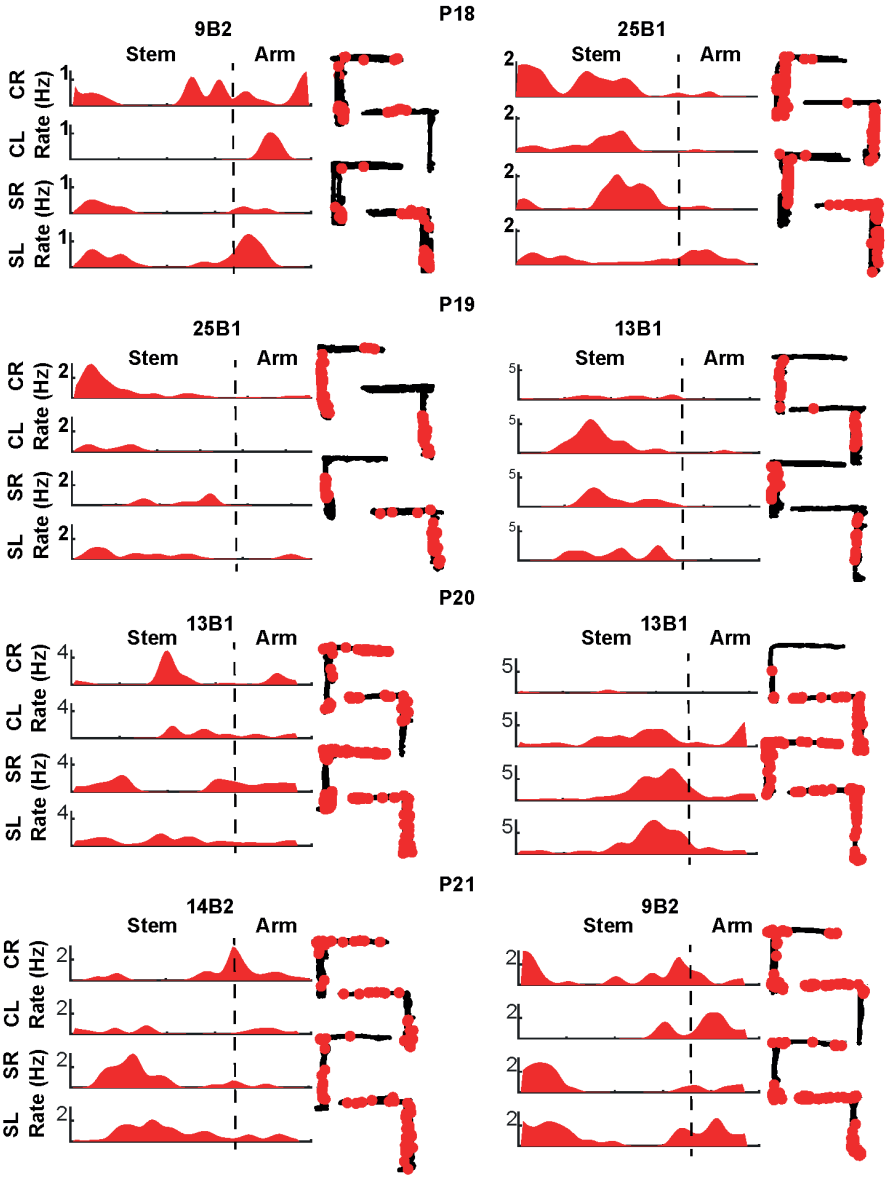


Figure S3.4. Part 1/3

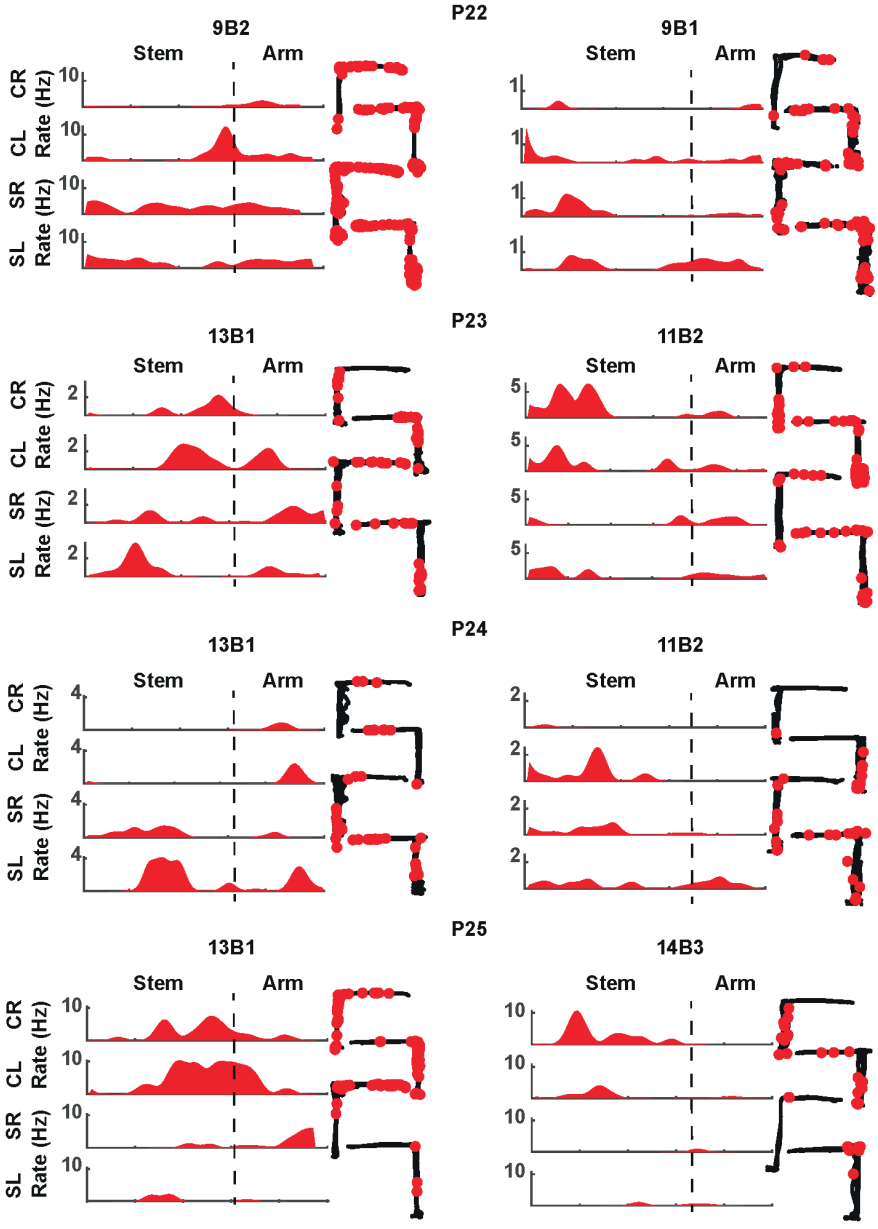


Figure S3.4. Part 2/3

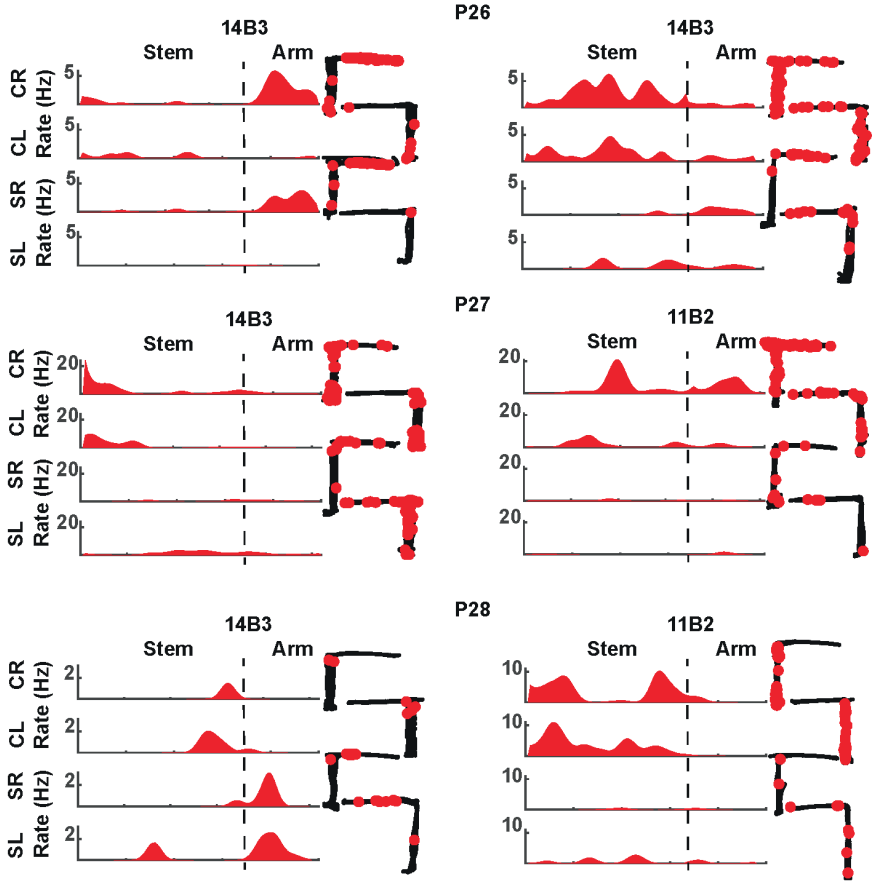


Figure S3.4. Representative place cell ratemaps for different post-natal days. Related to Figure 1. Left; linearised ratemaps for place cell activity on the T-maze. Note, each run type has its own ratemap. Right: raw spikes recorded during the different runs plotted against their spatial position on the maze. *CR = choice right run, CL = choice left run, SR = sample right run, SL = sample left run.

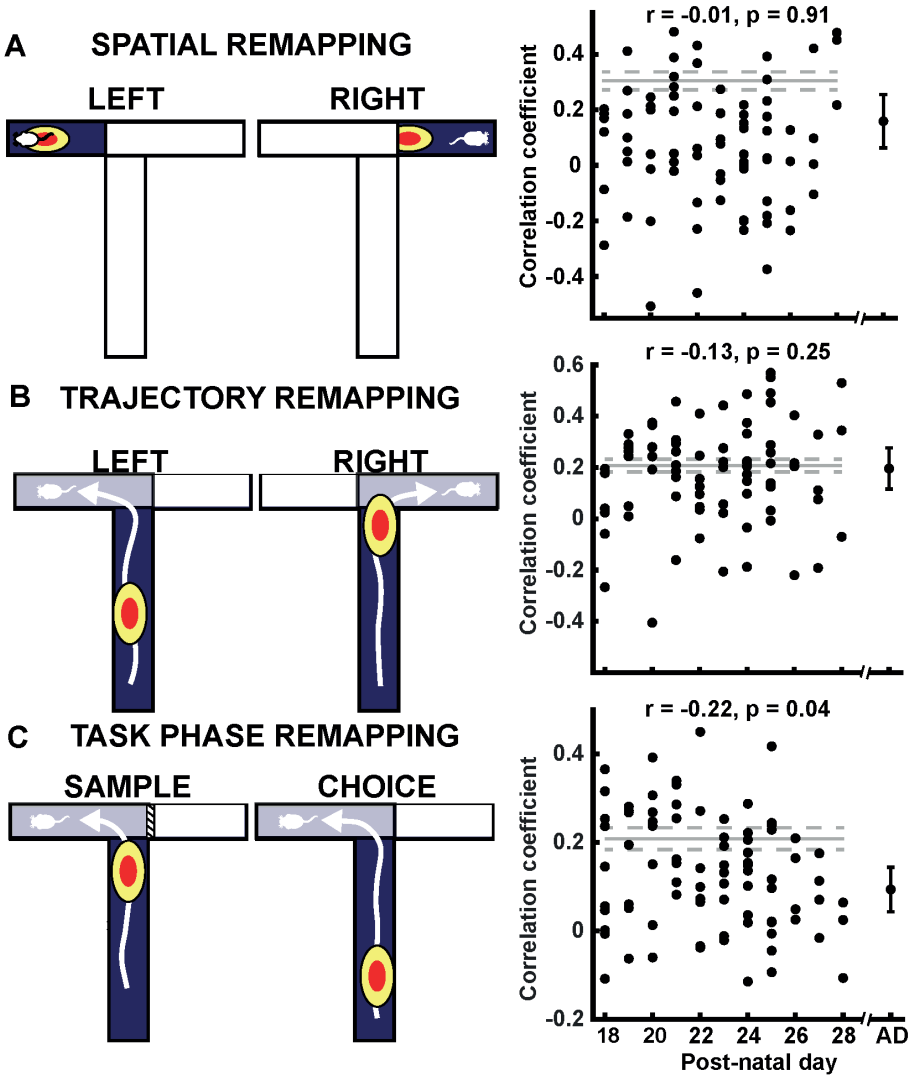


Figure S3.5. Development of place cell remapping with age. Related to Figure 2. (A) Left: Schematic of spatial remapping analysis (ratemap correlations between left and right arms). Right: Session mean spatial remapping vs post-natal age. (B-C) Same as A but for trajectory **(B)** and task phase remapping **(C)**.

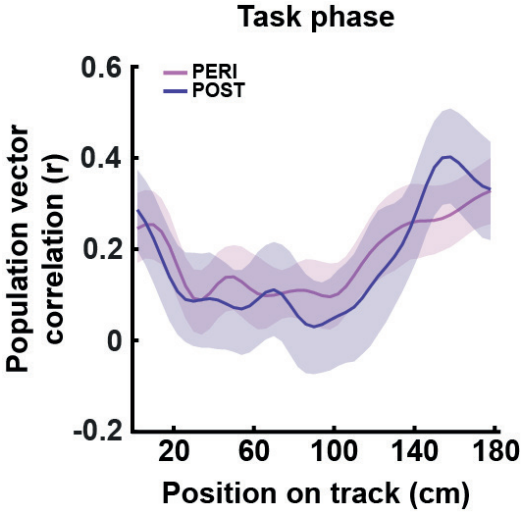


Figure S3.6. Task phase remapping emerges abruptly following inflection. Related to Figure 2. Population vector correlation between Sample and Choice ratemaps for two developmental periods post inflection. PERI = data recorded on the day of the inflection point and two subsequent days, POST = data recorded three or more days after the inflection point. Error bars show 95% confidence intervals.

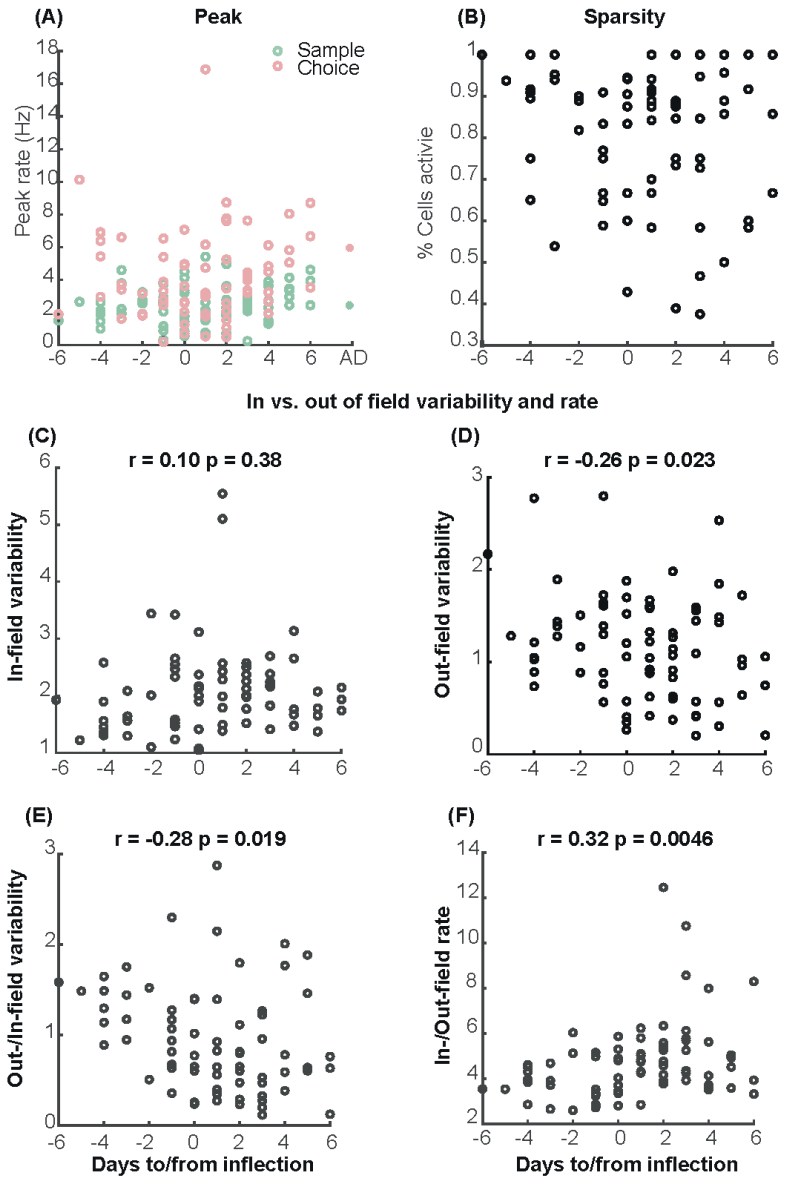


Figure S3.7. Developmental changes in place cell activity. Related to Figure 3. (A) Place field peak rate plotted against days to/from inflection. **(B-F)** Same as A but for sparsity **(B)**, within place field firing rate variability **(C)**, outside place field firing rate variability **(D)**, ratio between outside and within field variability **(E)**, and ratio between within and outside field rate **(F)**.

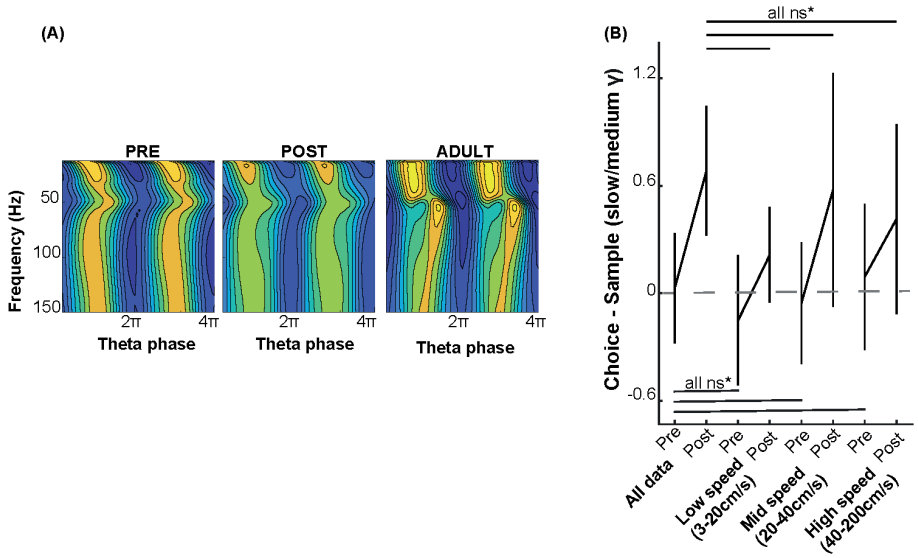
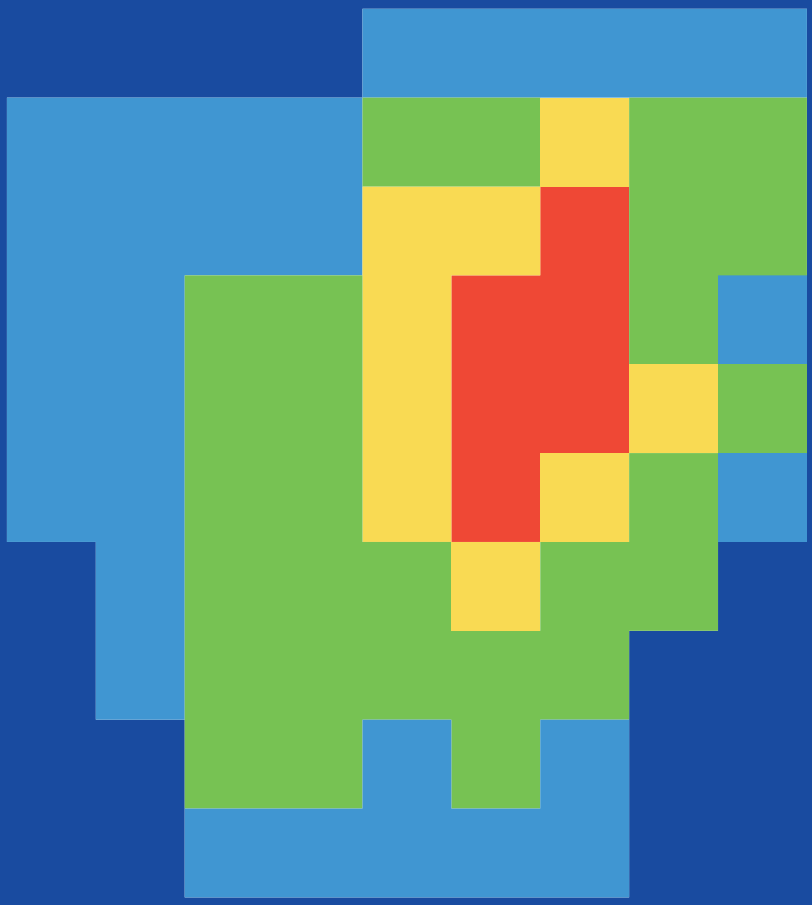


Figure S3.8. Phase-amplitude coupling during sleep and speed-band analysis of slow-to-medium gamma coupling during pre- and post-inflection periods. Related to Figure 4. (A) Cross-frequency coupling between theta-band and high frequency (>15Hz) oscillations during sleep. X-axis shows theta phase and y-axis frequency band. **(B)** Bootstrapped difference scores between slow-to-medium gamma ratios for sample and choice task phases. Far left: Original data. Left middle: data filtered for low speed. Right middle: data filtered for medium speed. Far right: data filtered for high speed. The difference scores during pre and post inflection periods for individual speed bands were compared with the difference scores seen in the original data. None of the speed bands revealed difference scores that deviated statistically from the original data.



Chapter 4

Population mechanisms underlying spatial working memory emergence

Summary

Objective

Hippocampus is thought to support learning and working memory (WM) capabilities. Specifically, the mechanism of hippocampal reactivations that occurs during sharp-wave ripples (SWR) has been put forward as a candidate driving mechanism of memory consolidation and planning (required for WM). However, no study until now has examined the role of hippocampal replay in the early life emergence of hippocampal memory.

Approach

We recorded CA1 place cell activity and local-field potential daily as rat pups aged between P17 to P28 performed a spatial working memory task.

Main results

SWR increased in duration as WM matured. Furthermore, we detected reactivation events which increased the granularity of their representations in coordination with WM emergence. We found that preferred reactivation of behavioural goals might be independent of WM. However, increased reactivations between subsequent trials predicted spatial WM emergence.

Significance

These results for the first time directly relate the maturation of hippocampal reactivations to memory emergence and provide preliminary support the proposed role of hippocampal replay in learning.

4.1 Introduction

Learning and working memory are crucially dependent on mature and healthy hippocampal function (Nadel & O'Keefe, 1978; Scoville & Milner, 1957; Spiers et al., 2001; Zola-Morgan & Squire, 1990). The results reported in the previous experimental chapter primarily focused on the development of single-cell encoding and retrieval mechanisms. In this chapter, I will report my findings on the development of hippocampal population mechanisms that support learning and memory. Sharp-wave ripples (SWRs) are a brief period of highly synchronous activity in the hippocampus that have been linked to learning and planning (Buzsáki, 2015; Buzsáki et al., 1992; Buzsáki & Vanderwolf, 1983). Place cells, the principal memory cell of the hippocampus, reinstate recent activity during SWRs in a process called hippocampal replay, which has been proposed to be the driving mechanism for learning in the hippocampus (Lee & Wilson, 2002; O'Keefe & Nadel, 1978; Pavlides & Winson, 1989; Wilson & McNaughton, 1994).

Disruption of sleep SWRs impairs learning in rodents, implying their direct causal involvement in learning processes (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). Disrupting awake SWR activity has also been shown to impair learning in spatial WM tasks without a delay (Jadhav et al., 2012) and with a delay (Zhang et al., 2021). Conversely, optogenetically extending the duration of SWRs has been shown to improve learning on a spatial WM task (Fernández-Ruiz et al., 2019). Increased occurrence of awake SWRs at reward locations in a spatial learning task has been shown to predict memory performance (Dupret et al., 2010). Whilst these studies established the causal role of awake SWRs in memory WM performance, the manner in which SWRs affect learning remains still somewhat elusive. One proposed and demonstrated function of awake SWRs was that they strengthen single place cell representations, and coordinated activity of pairs of place cells with correlated place fields (O'Neill et al., 2006).

Place cells that encode nearby spaces and therefore frequently co-activate during wakeful behaviour also tend to re-activate together during SWRs (Pavlides & Winson, 1989). Hippocampal replay is reactivation of multiple place cells in sequences which match paths traversed during wakeful behaviour (Lee & Wilson, 2002). Replay occurs at compressed timescales thought to be conducive to synaptic plasticity (Nádasdy et al., 1999). Since replay tends to represent behaviourally salient information such as paths to rewards, it is thought to play an important role in learning (Singer & Frank, 2009; Wilson & McNaughton, 1994). Supporting this hypothesis, a recent study has causally linked distinct replay sequences to learning of specific environments (Gridchyn et al., 2020). However, replay can also occur

during consummatory or rest periods during wakeful behaviour and reactivate paths to rewarded locations (Foster & Wilson, 2006b; Pfeiffer & Foster, 2013a; Singer et al., 2013a). Awake replay is thought to serve a potential role in planning and decision making crucial for working memory in addition to supporting learning through memory consolidation (Ólafsdóttir et al., 2018).

As discussed in previous chapters, hippocampal memory develops significantly in the fourth postnatal week. The sharp wave emerges in the first week of life (Leinekugel, Khazipov, Cannon, Hirase, Ben-Ari, & Buzsáki, 2002), whereas the ripple component matures in the third week of life (Buhl & Buzsáki, 2005). Hippocampal replay has been detected as early as P17, however early replay sequences recapitulate short and mostly stationary trajectories (Farooq & Dragoi, 2019; Muessig et al., 2019b). The earliest observed replay sequences tend to depict stationary or short trajectories, whereas in the fourth week of life replay sequences extend over larger distances and begin resembling adult-like activity (Muessig et al., 2019b). However, no study to-date has investigated the emergence of hippocampal reactivations during awake periods nor their emergence in relation to the maturation of hippocampal memory.

The aim of this study was to investigate how the development of SWRs and hippocampal reactivations relates to sudden spatial WM emergence. To this end, we combined in-vivo extracellular electrophysiology in freely moving developing rats with behavioural experiments using a spatial WM task.

4.2 Results

We recorded local field potential (LFP) and ensembles of CA1 principal neurons in 13 chronically implanted rat pups aged P17-P28. The pups performed a working DNMP memory task (see Chapter 3 for a detailed description of the task), which was immediately followed by a sleep session (mean duration = 59.5min (SD=10.23), Figure S4.1B). Sigmoid curves were fitted to developmental curves on the T-maze task to identify the age of inflection for individual animals (i.e. when memory capability on this task emerged, on average at P22, Chapter 3).

4.2.1 Sleep SWR duration increases in tandem with spatial WM maturation

In the first instance, we characterised the development of SWR events, detected both during still periods of Awake behaviour during the task (i.e. movement speed ≤5cm/s), as well as throughout the Sleep sessions (Methods). We observed no changes in the prevalence of SWR events in relation to WM memory maturation and the SWR incidence rates did not differ between Awake and Sleep periods (Awake = 0.52 events

per second (SD=0.14), r = -0.016, p = 0.9, Sleep = 0.48 events per second (SD=0.11) r = 0.049, p = 0.68, $t_{(142)}$ = 1.75, p = 0.082, Figure 4.1A). Further, the proportion of cells active during Awake SWR events did not change with age. Overall, the proportion of cells active during Sleep SWRs was significantly higher than during Awake SWRs (Awake = 0.049 (SD=0.032), r = 0.12, p = 0.29, Sleep = 0.071 (SD=0.048), r = 0.19, p = 0.087, $t_{(170)}$ = 3.62, p = 0.00039, Figure 4.1B).

Recently, SWR duration has been causally implicated in spatial working memory as artificial prolongation of SWRs has been shown to improve WM performance (Fernández-Ruiz et al., 2019). Therefore, we hypothesised that the duration of SWRs may positively correlate with the emerging ability to carry out the spatial WM task in our study. Mean duration of Sleep SWR events was significantly lower than the average Awake SWR. However, whilst Awake SWR events did not undergo developmental changes in duration, Sleep SWR events significantly increased in duration as the animals' capability to perform the memory task emerged (Awake = 75.51ms (SD=6.21), r = -0.012, p = 0.92, Sleep = 66.082ms (SD=4.09), r = 0.31, p = 0.0043, $t_{(151)}$ = 11.23, p < 0.0001, Figure 4.1C). The average instantaneous frequency of Awake and Sleep SWR events did not differ. However, Awake SWR events exhibited a decline in mean instantaneous frequency that correlated with maturation of the ability to carry out the task. Sleep SWR events did not significantly change in mean instantaneous frequency with working memory maturation (Awake = 165.27ms (SD=3.23), r = -0.27, p = 0.019, Sleep = 165.39ms (SD=3.38), r = -0.1, p = 0.4, $t_{(157)}$ = 0.23, p = 0.82, Figure 4.1D).

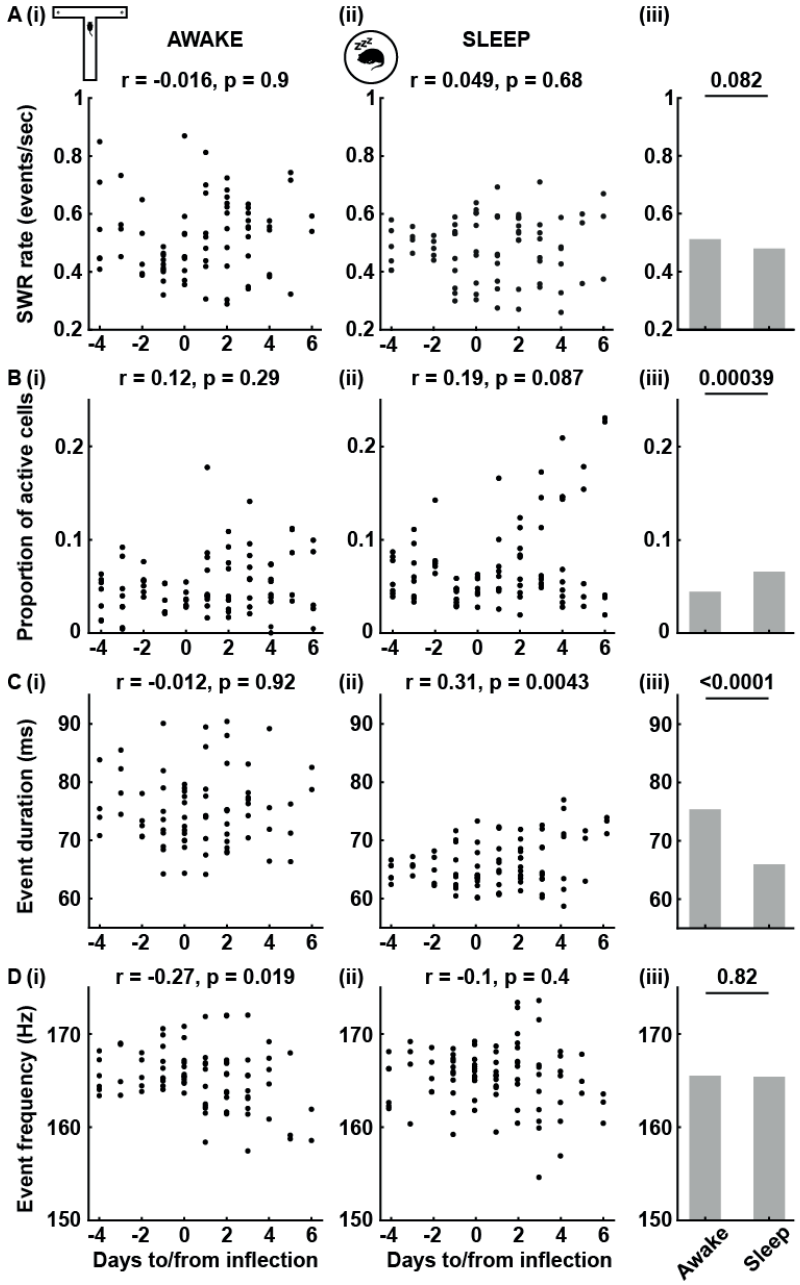


Figure 4.1. Early post-natal development of awake and Sleep SWRs. (A) Mean (i) Awake and (ii) Sleep SWR incidence rate (events per second) per session as a function of days to/from the inflection point. (iii) mean Awake (left) and Sleep (right) SWR incidence rates; numbers indicate paired T-test p-values. **(B-D)** Same as A but for proportion of cells recorded in a session that were active during detected SWR events, duration of SWR events (milliseconds), and event instantaneous frequency (Hz).

4.2.2 Increased density of reactivations predicts spatial WM maturation

Next, we sought to investigate the development of hippocampal reactivations during SWRs. We detected periods of increased (>3SD) multiunit activity during SWRs and labelled these candidate reactivation events (Methods). Then we used a Bayesian decoding approach to determine the probability of the animal's location given the single unit activity during candidate events (Methods). We then randomly shuffled the identity of the cells in the event and decoded the location of 100 such shuffles. Comparing the average maximum posterior probability for all decoding bins of candidate replay events to that of the shuffle distribution allowed us to identify reactivation events that showed better location decoding than chance. Since place cell activity was modulated by the task phase (Sample vs Choice) in our task (Chapter 3), we decoded all four run types (i.e. Sample left, Sample right, Choice left, Choice right) separately and computed the mean maximum posterior probability of location decoding across the event for each run type in order to determine which run type was reactivated (Methods). The identified run type event was submitted for further analyses. Given the recent evidence demonstrating that in early life hippocampal replay tends to progress from mostly static reactivations in the third post-natal week to reactivation of multiple locations over long trajectories in the fourth post-natal week (Muessig et al., 2019b), our goal was to relate this finding to memory maturation. In order to quantify the average number of locations represented in each session, we detected local peaks in the posterior probability density of each reactivation event in a given session (Figure 4.2A, Methods).

The number of locations reactivated by an average Awake reactivation event depicting the Sample task phase significantly increased with WM maturation ($r = 0.43$, $p = 0.042$). Conversely, Awake reactivation events representing the Choice task phase did not change with memory maturation ($r = 0.23$, $p = 0.29$). There was no difference in the number of locations reactivated between Awake Sample and Choice events (Sample = 2.69 (SD=0.59), Choice = 2.43 (SD=0.47); $t_{(44)} = 1.66$, $p = 0.1$, Figure 4.2B). Similarly, Sleep reactivation events representing the Sample task phase robustly increased the number of locations reactivated as spatial WM matured ($r = 0.44$, $p = 0.017$), whereas Choice reactivation events did not change with memory maturation ($r = 0.19$, $p = 0.31$). Further, there were significantly more locations reactivated during Sample events than during Choice events in Sleep (Sample = 2.82 (SD=0.46), Choice = 2.43 (SD=0.42); $t_{(56)} = 3.4$, $p = 0.0012$, Figure 4.2C).

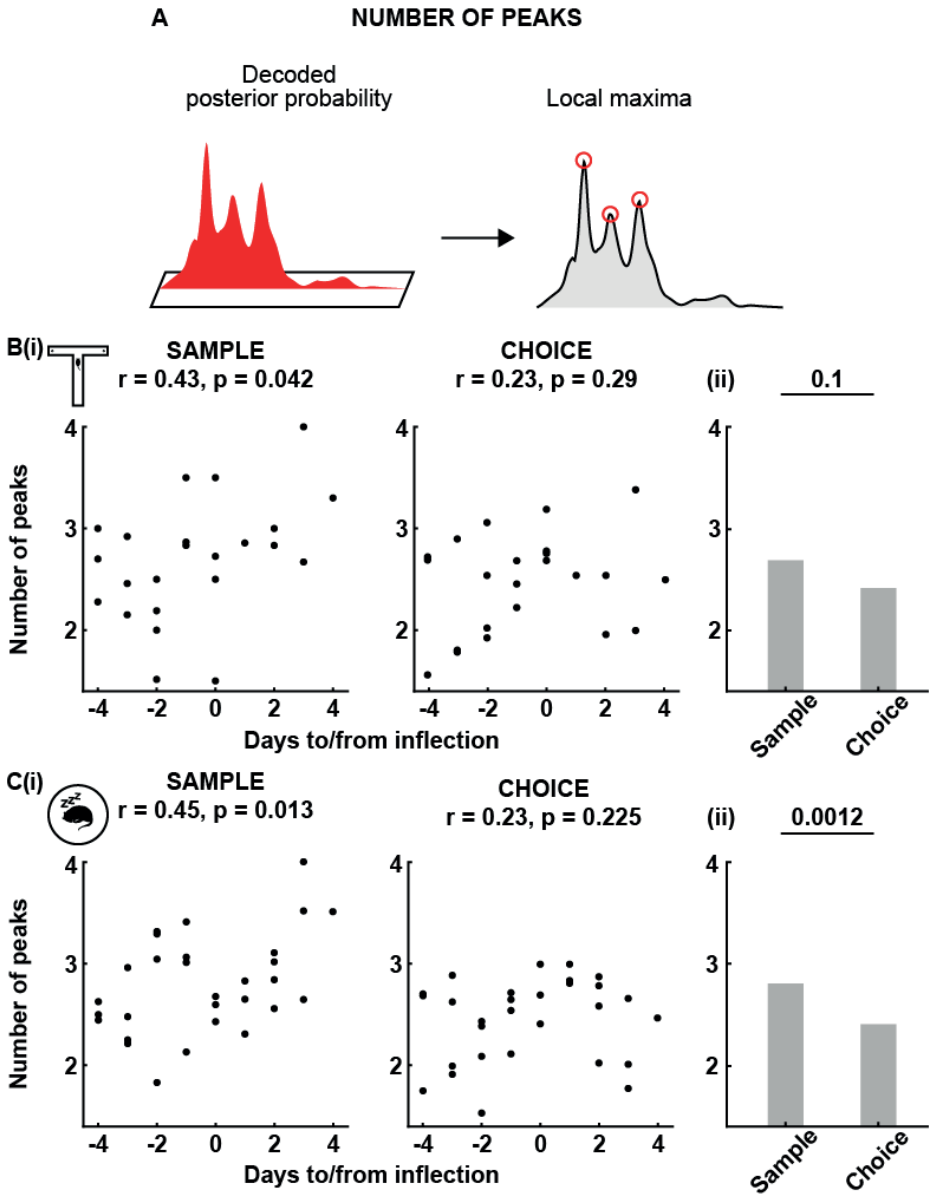


Figure 4.2. Developmental changes in the number of reactivated locations. (A) Schematic of the number of peaks analysis, red circles indicate local maxima (peaks). **(B)** (i) Mean number of reactivated peaks per session in Sample and Choice reactivation events as a function of days to/from the inflection point. (ii) Mean number of reactivation peaks in Sample (left) and Choice (right) Awake reactivation events. **(C)** Same as panel B, but for Sleep reactivation events.

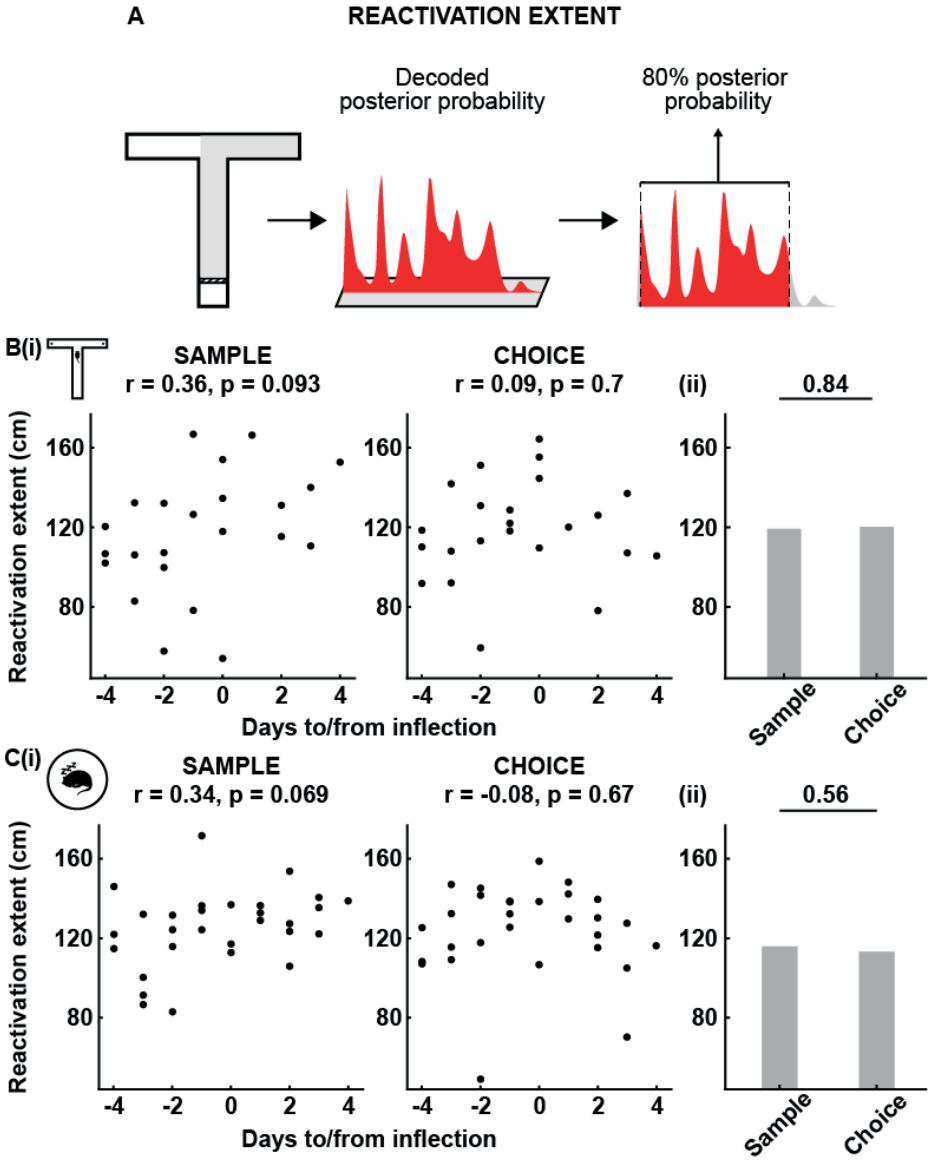


Figure 4.3. Developmental changes in the extent of the track reactivated. (A) Schematic of the reactivation extent analysis, red histogram denoting the density of decoded posterior probability on a linearised track. **(B)** (i) Mean extent of the track (cm) that captures 80% of the posterior probability density in Sample (left) and Choice (right) Awake reactivation events. (ii) Mean number of reactivation peaks in Sample (left) and Choice (right) Awake reactivation events; number indicates paired T-test p-value. **(C)** Same as panel B, but for Sleep reactivation events.

As a complementary approach, we calculated the extent of the track that comprised 80% of the decoded posterior probability density (Figure 4.3A, Methods). The results followed the trends observed for the number of peaks analysis, but did not reach significance. In Awake reactivations of the Sample task phase, the extent of the track reactivated tended to be longer Post-inflection than Pre-inflection, but this effect was not significant ($r = 0.36$, $p = 0.09$). Little change was observed in the Awake reactivations of the Choice task phase ($r = 0.091$, $p = 0.68$), and there was no significant difference between the Sample and Choice task phase reactivation extent (Sample = 117.15cm (SD=30.29), Choice = 118.81cm (SD=24.81), $t_{(44)} = 0.2$, $p = 0.84$, Figure 4.3B). There was also a tendency for Sleep reactivations of the Sample task phase to increase in spatial extent with spatial WM maturation, though the effect was marginally not significant ($r = 0.34$, $p = 0.069$). No change was observed for the Sleep reactivations of the Choice task phase ($r = -0.081$, $p = 0.67$), and Sleep reactivations of Sample and Choice task phases did not differ in spatial extent (Sample = 123.68cm (SD=17.28), Choice = 120.82cm (SD=20.95), $t_{(58)} = 0.58$, $p = 0.56$, Figure 4.3C).

4.2.3 Replay favours reward locations and may support memory maintenance

The foregoing results suggest that during development, hippocampal reactivations might undergo some changes in their content. Therefore, we investigated what section of the track was reactivated the strongest. To this end we divided the track into three equal divisions: first half of the T-maze stem (Stem), second half of the stem including the arm intersection (Approach), and arm (Arm) (Figure 4.4A). In each of the track divisions we summed the decoded posterior probability of the animal's location based on the spiking activity during reactivation events in order to identify which section was reactivated the strongest. Events reactivating Sample and Choice task phases were analysed separately.

First, we report the analysis of Awake reactivation events. Reactivations of the Sample task phase predominantly concentrated on the Arm section over Stem or Approach sections. Whereas reactivations of the Choice task phase preferentially reactivated both Stem and Arm sections over the Approach. (Sample: Stem = 0.26% (SD=0.16), Approach = 0.26% (SD=0.16), Arms = 0.48% (SD=0.21), Stem vs Approach: $t_{(34)} = 0.073$, $p = 0.94$, Stem vs Arms: $t_{(34)} = 3.51$, $p = 0.0013$, Approach vs Arms $t_{(34)} = 3.56$, $p = 0.0011$; Choice: Stem = 0.33% (SD=0.18), Approach = 0.23% (SD=0.12), Arms = 0.44% (SD=0.18), Stem vs Approach: $t_{(44)} = 2.26$, $p = 0.029$, Stem vs Arms: $t_{(44)} = 1.96$, $p = 0.057$, Approach vs Arms $t_{(44)} = 4.64$, $p < 0.0001$, Figure 4.3B). We performed the same analysis for Sleep reactivations events. The results for the reactivation events representing the Sample task phase match the results observed in Awake analysis.

Namely, most of the decoding was concentrated on the Arm section of the track, and there was no difference between Stem and Approach sections. Sleep reactivation events of the Choice task phase concentrated on the Arm section significantly more than the Stem or Approach sections, and the Stem section significantly more than the Approach section (Sample: Stem = 0.27% (SD=0.14), Approach = 0.29% (SD=0.13), Arms = 0.44% (SD=0.17), Stem vs Approach: $t_{(47)} = 0.64$, $p = 0.53$, Stem vs Arms: $t_{(47)} = 3.86$, $p = 0.00035$, Approach vs Arms $t_{(48)} = 3.44$, $p = 0.0012$; Choice: Stem = 0.33% (SD=0.18), Approach = 0.23% (SD=0.13), Arms = 0.44% (SD=0.2), Stem vs Approach: $t_{(57)} = 2.58$, $p = 0.013$, Stem vs Arms: $t_{(57)} = 2.24$, $p = 0.029$, Approach vs Arms $t_{(58)} = 5.021$, $p < 0.0001$, Figure 4.3C). However, despite these biases in where replay was concentrated there were no significant developmental effects (Table S4.2).

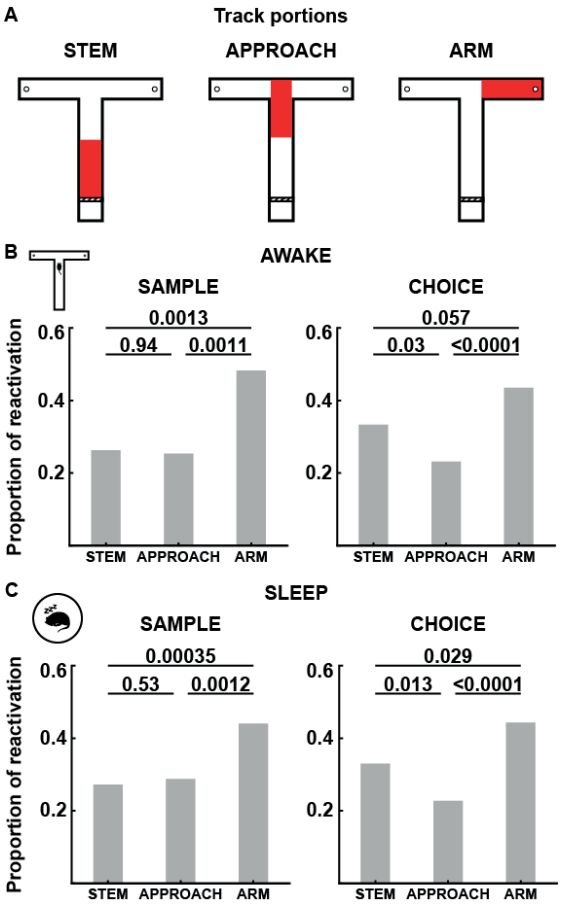


Figure 4.4. Density distribution of reactivated location posterior probability. (A) Schematic of the T-maze with red areas highlighting the three equal sections of the track. **(B)** Mean proportion of the Awake reactivation event posterior probability density divided into the three track sections; numbers represent paired t-test p-values. **(C)** Same as panel B but for Sleep reactivation events.

Awake replay has been implicated in planning. Successful completion of our task requires planning, but only during specific temporal epochs. To further investigate the role of awake replay development in WM maturation, we analysed reactivations during three time periods in the task (Figure 4.5A): during Sample or Choice runs on the track (Run), during the 15s delay period between subsequent Sample and Choice runs (Delay), and during the 30-45s inter-trial interval between two subsequent trials (ITI). If reactivations supported planning, then we would expect them to occur more frequently during the Delay, and during the Choice Run periods. Additionally, we would expect to observe this increase at or after the inflection point of spatial WM.

First, we report developmental changes in when sample phase reactivations occurred during the task. A strong decrease in the amount of reactivation occurring in the Run period, and a strong increase in reactivations occurring in the ITI period coincided with spatial WM maturation. The proportion of reactivation events that occurred in the Delay period remained stable (Run $r = -0.65$, $p = 0.0007$, Delay $r = -0.012$, $p = 0.96$, ITI $r = 0.63$, $p = 0.0014$, Figure 4.5B). We performed the same analysis for Awake reactivations of the Choice task phase. These results corroborate the robust reduction in the amount of reactivation events during the Run period coincident with memory maturation. However, there was no increase in the proportion of events occurring in neither the Delay or ITI periods (Run $r = -0.58$, $p = 0.0037$, Delay $r = 0.35$, $p = 0.11$, ITI $r = 0.26$, $p = 0.24$, Figure 5C).

The Delay (15 seconds) and ITI (30-60 seconds) periods of the task are of set duration throughout the experiment. However, the duration of the Run period systematically changes as animals tend to increase their running speed and complete the task faster as they get older and the ability to carry out the task emerges (Figure S4.1A). Therefore, in order to control for the variation in the duration of the Run periods, we divided the number of events by the total duration of the Run period in each trial. Even when accounting for the duration of Run periods, we observed a significant decrease in the incidence rates of reactivation events in relation to spatial WM maturation. This effect replicated for both Sample and Choice reactivation events (Event rate $r = -0.49$, $p = 0.018$, Sample Pre = 0.73 (SD=0.86), Post = 0.025 (SD=0.08), $t_{(21)} = 2.56$, $p = 0.018$, Choice Pre = 1.3 (SD=1.16), Post = 0.22 (SD=0.23), $t_{(21)} = 2.86$, $p = 0.0094$, Figure S4.3).

Taken together, the results of these analyses show that WM maturation coincides with an abrupt increase in the density of reactivations (i.e. more reactivated locations in the same amount of space). Furthermore, when the animals develop the ability to distinctly represent the Sample and Choice task phases (Chapter 3),

the content of their reactivations also diverges (i.e. predominantly arms in Sample reactivations, increased reactivation of both start of the track and arms in Choice reactivations). Finally, with the emergence of WM, occurrence of reactivations nearly completely ceases on the track, and instead reactivations primarily occur in the ITI box after completion of a trial.

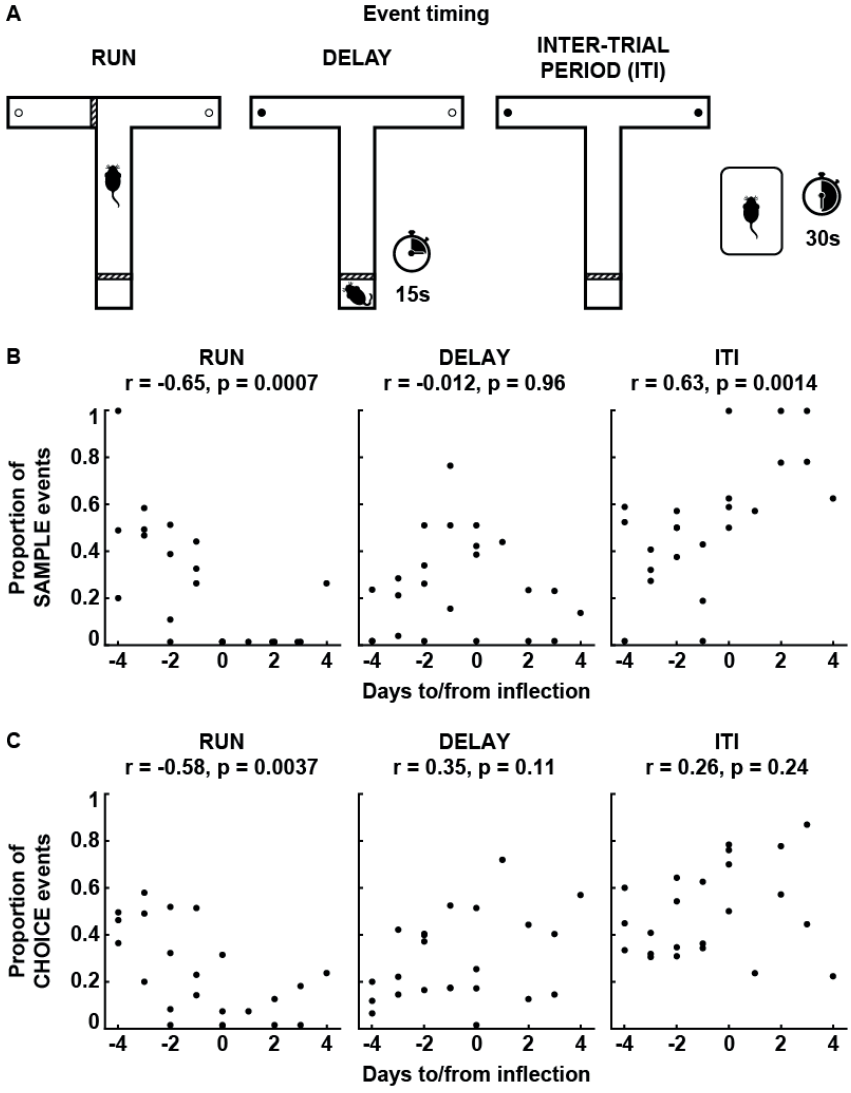


Figure 4.5. Developmental changes in the timing of reactivation events. (A) Schematic representing the three distinct periods during which reactivation events could occur. **(B)** Proportion of the total number of Sample reactivation events per session that occurred in the three distinct periods of the task as a function of days to/from the inflection point. **(C)** Same as panel B but for Choice reactivation events.

4.3 Discussion

We have for the first time directly charted the development of hippocampal reactivations to hippocampal memory emergence. We found that although the general incidence rate of SWRs remains stable during development, memory emergence is accompanied by an increase in recruitment of place cells in the Sleep SWR events and subsequent lengthening of average Sleep SWR events. Furthermore, we found a developmental increase in the number of locations reactivated during SWR events, and this effect was specific to Sample task reactivations. Taken together, these results indicate that the specific content of reactivations rather than the number of reactivation events may contribute to the developmental emergence of hippocampal memory. Furthermore, spatial WM maturation was associated with a strong reduction in reactivations on the track, had no influence on reactivations in the delay period, but was accompanied by a strong increase in reactivations after each trial. Thus, these findings suggest that although reactivations develop in tandem with working memory, it is not clear if these developmental changes directly relate to the working memory demands of the task. Hopefully future studies, which test different facets of hippocampal memory development, may be able to identify the precise role of replay development.

SWRs are known to mature rapidly between post-natal days P12 to P18 (Buhl & Buzsáki, 2005; Pochinok et al., 2024). Our results match these findings in terms of instantaneous frequency which is at adult levels from the earliest ages in our experiment (P17). However, our data implies that SWRs do undergo further functional maturation in 3rd and 4th postnatal weeks. We found that lengthening of sleep SWRs correlates with the emergence of spatial working memory. This finding is supported by adult studies that have demonstrated that shortening SWRs negatively impacts learning (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009; Jadhav et al., 2012), as well as evidence showing that prolonged SWRs promote learning (Fernández-Ruiz et al., 2019). Therefore, hippocampal memory emergence might depend on protracted functional maturation of SWRs after their initial emergence.

The development of hippocampal reactivations and particularly how their development relates to the emergence of hippocampal memory has not been studied extensively. Recent years have seen initial evidence of hippocampal replay emerging in the same period that hippocampal memory is known to emerge in rats (Farooq & Dragoi, 2019; Green & Stanton, 1989b; Muessig et al., 2019b). The results from these studies suggest that the earliest replay events tend to depict stationary or short trajectories, and only begin replaying extended trajectories resembling

adult replay in the fourth week of life. Our results lend further support to these developmental findings as we showed that the number of locations reactivated increased as memory emerged in our task. In previous work (see Chapter 3) we showed place field size strongly negatively correlates with maturation of the ability to perform the task used in this study, indicating that WM maturation coincides with increased spatial coding precision (Bevandić, Stella, et al., 2024). Defined in this way, maturation of place cell specificity could underlie the observed increase in number of locations reactivated. However, we found no developmental increase of the extent of the track reactivated. Our results might therefore suggest that density of replay trajectories, instead of their length, functionally relates to spatial WM maturation. There is recent evidence supporting this interpretation. Berners-Lee et al. (2022). observed that with increased experience replay trajectories increase in duration but not in spatial extent, thereby taking longer time to recapitulate the same space in more detail by adding multiple smaller locations to the reactivation.

Another crucial aspect of our approach is the ability to assess task-phase related differences in the results, which we know affect place cell activity robustly (Bevandić, Stella, et al., 2024). We only observed a developmental increase in the number of locations reactivated during the reactivation of the Sample phase of our task, whilst the reactivation of the Choice phase remained largely unchanged. The Sample phase is the phase in which the animal receives information which it needs to hold in working memory in order to make the correct turn in the subsequent Choice phase. Taken together, these results would seem to suggest that the emergence of spatial WM is dependent on hippocampal reactivations that support the coding of information necessary for accurate performance on a WM task.

Existing literature shows that awake replay can vary in content depending on task demands (Ólafsdóttir et al., 2017). Literature shows that hippocampal replay can reactivate paths towards reward locations, as well as predominantly cluster around reward locations (Dupret et al., 2010; Pfeiffer & Foster, 2013a; Singer & Frank, 2009). We found that replay events in our task consistently reactivated the arms of the track the most, indicating reactivations were clustered around reward locations in our task. Interestingly, this clustering bore no relation with WM development, suggesting this representational aspect of replay may not impact hippocampal memory development.

The exact function of awake replay is still a matter of debate. It has been suggested that in addition to memory consolidation, awake replay might play a role in planning and decision making (Dragoi & Tonegawa, 2011; Foster & Wilson, 2006b;

Ólafsdóttir et al., 2018). However, multiple studies have failed to relate awake replay to current behaviour, instead finding that awake replay can represent remote, immediately irrelevant locations, or entirely different environments (Davidson et al., 2009; Gupta et al., 2010; Karlsson & Frank, 2009a). In our task, the emergence of spatial WM memory was associated with reduced replay during the task. Additionally, increased occurrence of replay events between two subsequent trials (i.e. after the animal has made a choice) predicted WM emergence. Therefore, our results may be interpreted as potentially going against the hypothesis that awake replay serves the function of planning.

In conclusion, this study for the first time directly related the development of SWRs and hippocampal reactivations to the emergence of spatial WM. Our results suggest that presence of hippocampal reactivations may not in itself be sufficient for the emergence of memory. Rather, further increase in duration of reactivations and density of reactivated locations may be important for spatial WM emergence. What aspects of WM development these neuro-developmental changes serve, or whether they support complementary aspects of hippocampal memory, remains a question for future research to address.

4.4 Methods

Experimental subjects

Thirteen Lister Hooded rat pups (30-52g at implantation) underwent a surgical procedure to implant a microdrive carrying eight or sixteen tetrodes of twisted 17µm HM-L coated 90% platinum, 10% iridium wire (California Fine Wire), targeting the right CA1 (ML: 2.0-2.3mm, AP: 3.0mm posterior to bregma). Electrode tips were gold plated to reduce impedance to 150-300kOhm at 1kHz. Pups were allowed to recover from surgery for 48h. Pups were housed together with the dam (until weaning) and littermates on a reversed 12-h light-dark cycle, and always had ad libitum access to water and food.

Electrophysiological recording

After the post-operative recovery period, electrophysiological activity was screened two to three times a day. All recordings were performed using an Axona recording system (Axona Ltd., St. Albans, UK) which recorded spike-threshold triggered single unit activity, continuous LFP, and position data. Each channel was amplified 5000 – 15000 times and recorded referenced to another channel on a separate tetrode. Spikes and LFP were sampled at 48KHz. Animal position was determined using an overhead infrared (IR) camera recording the location of an array of IR

light-emitting diodes (LED) mounted on the headstage. Tetrodes were gradually advanced ventrally in 62.5 – 125μm steps, at least 3h apart, until place cells and sharp-wave ripples were detected.

Place cell detection

All single unit analyses were restricted to putative principal cells, identified by manual inspection of waveforms across the entire recording session. KlustaKwik was applied to spike-thresholded data to sort the data into clusters and then the clusters were manually curated in Tint (Axona Ltd.). We classified spike sorted neurons as place cells by computing Skaggs Information (bits per second), and compared the value we obtained against a null distribution generated by random permutations of spike times. Cells that exceeded 95th percentile of their own shuffle were deemed place cells. Sessions containing fewer than five cells with significant Skaggs information values were excluded from analysis.

Sharp-wave ripple detection

We first detected the EEG channel with the highest theta (6-12Hz) to broadband (20-150Hz) power ratio. Any sessions that had no EEG channel with a theta-to-broadband power ratio higher than 1 were excluded from the analysis. We filtered the LFP data from the best channel in the ripple band (150-250Hz) and calculated the instantaneous power and frequency. We then identified periods where the instantaneous power of the LFP signal exceeded the 97.5 percentile threshold. The start and end points of the putative SWR event were determined by the points where the instantaneous power exceeds and falls below the median power, respectively. Any events shorter than 40ms or longer than 500ms were excluded. For Awake replay events, events that occurred when the animal's speed exceeded 5cm/second were excluded.

Reactivation event detection

First, we identified periods of increased multi-unit activity (MUA) by creating a histogram (1ms bins) of all putative place cells in a session and smoothing it (Gaussian kernel 20ms, sigma = 5ms). Then we detected periods when MUA rate passed 3 standard deviations above the mean. Start and end of the event were defined by the points at which the MUA rate exceeded or fell below the mean MUA rate. Any events that occurred within 40ms of each other were merged into a single event. Any events that were shorter than 40ms or longer than 500ms were excluded. Next, we identified putative SWR events (see Sharp-wave ripple detection), and identified the events that passed both SWR and MUA criteria as putative reactivation events.

Decoding location during reactivation events

First, we divided the place cell activity into the four run types (i.e. sample left, sample right, choice left, choice right), and created separate ratemaps for each run type (i.e. four ratemaps per cell). For each putative reactivation event, we identified place cells active during the event. If there were fewer than 5 cells active during an event, the event was excluded from the analysis.

Next, we used a Bayesian approach to decode the posterior probability of the animal's location given the spiking activity of the place cells during the event:

$$P(x|k) = \prod_{i=1}^{N} \frac{T_{\alpha_i}(x)^{k_i}}{k_i!} exp^{-T\alpha_i(x)}$$

where the posterior probability P of the location x, given the population spiking activity K is determined by the ratemaps $\alpha_i(x)$, and number of spikes k fired by each cell i in time bins of T = 10ms. This results in spatial bin x time bin posterior probability matrix for each event, normalised to sum to 1.

For each decoded event we removed time bins that contained no posterior probability. First, we computed the maximum posterior probability in each time bin. Decoding quality was defined as the mean of maximum posterior probabilities across all time bins of the event. To assess if the reactivation event had better spatial decoding than expected by chance we used a cell ID shuffle, where relationship between cell ID and ratemaps was randomly permuted. For each shuffle we repeated the decoding analysis. For each even we generated 100 shuffles. Finally, we compared the real data to the shuffled data. If the real data exceeded the 95th percentile of the shuffle distribution, then the event was considered significant, and was permitted to further analyses. This procedure was performed separately for each of the four run types. To identify the run type that was reactivated most strongly, for we identified the run type with the highest decoding quality. Thus, for each event only one run type reactivation was submitted for further analyses.

Detecting decoding peaks

Any Awake sessions with <10 significant reactivation events and Sleep sessions with <50 significant reactivation events were excluded from the analysis. For each event we computed the decoded posterior probability density by summing the posterior probability across time bins. This results in a histogram of posterior probabilities across spatial bins representing the track. For each event we filtered out local maxima that are lower than 10% of the peak of the probability density. Five empty

spatial bins were added to the start and end of the track in order to be able to detect local maxima at the margins of the track. Then the probability density was smoothed by a boxcar filter with a size of 10 bins. Local maxima were detected using the in-built MATLAB function *islocalmax* with the minimum prominence threshold of 0.01 from the neighbouring local minima from each side or 0.005 from zero. After excluding local maxima of insufficient prominence or minimum height, we counted the number of detected local maxima as the number of reactivation peaks.

Spatial extent analysis

For this analysis exclusively the decoding was performed using a 30ms sliding window to compute the posterior probability of location. This effectively smooths the histogram of posterior probabilities with the goal of improving the accuracy of finding the interval which comprises 80% of the posterior probability density. Normalised posterior probability histograms were generated in the same way as with the peaks analysis. For each significant reactivation event we divided the posterior histogram into 1000 steps and then continuously summed the decoding across an increasing extent of the track in 1/1000 increments until the sum reached 80% of the total posterior density. We determined the spatial extent of reactivation by computing the difference in spatial bins of the limits comprising 80% of the posterior density.

Reactivated sections analysis

Normalised histograms of posterior probability densities were computed the same way as in the decoding peaks analysis. The spatial bins were then divided into three equal thirds representing the Stem, Approach, and Arm sections. We then summed the posterior density in each section and divided it by the total posterior density in order to calculate the proportion of posterior density concentrated in each section of the track.

Reactivation timing analysis

Normalised histograms of posterior probability densities were computed the same way as in the decoding peaks analysis. During the experiment, the experimenter marked the start and end timestamps of each trial with a remote control. These timestamps were later manually verified by rewatching the footage. Based on this data, for each session we extracted the timestamps and durations of periods when the animal was freely moving on the track (Run), waiting in the delay box (Delay), and waiting in the inter-trial interval box between subsequent trials (ITI). We compared the timestamps of detected reactivation events to these periods in order to classify in which period the event occurred. We divided the number of events that occurred in each period by the total duration of the period in order to control for differences in duration.

Statistical analyses

All the correlations reported in the study represent the Pearson correlation coefficient with corresponding p-value. All the significance tests of group means reported in the study represent the results of paired samples T-tests. The inflection point is defined as day 0, therefore all Pre groups represent data from -4 to -1 days to/from inflection, and all Post groups represent data from 0 up to 6 days to/from inflection.

4.5 Supplementary material

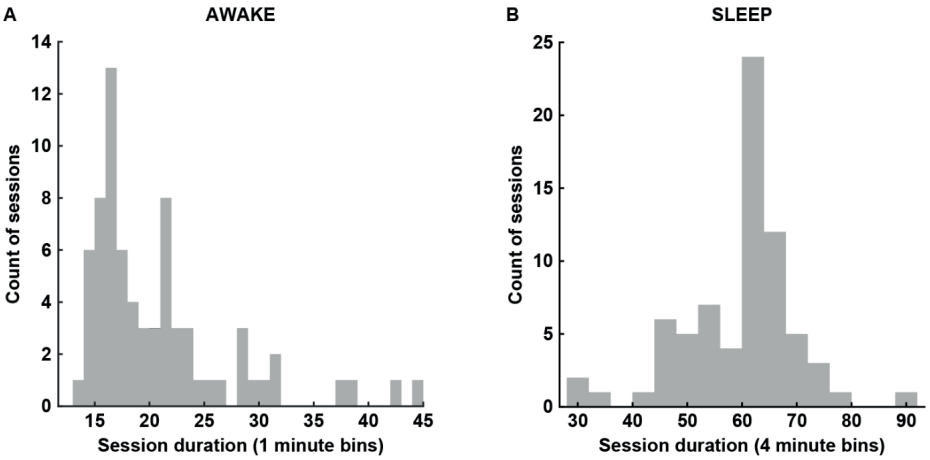


Figure S4.1. Mean session duration. (A) Distribution of Awake session durations (60 second bins). **(B)** Distribution of Sleep session durations (240 second bins).

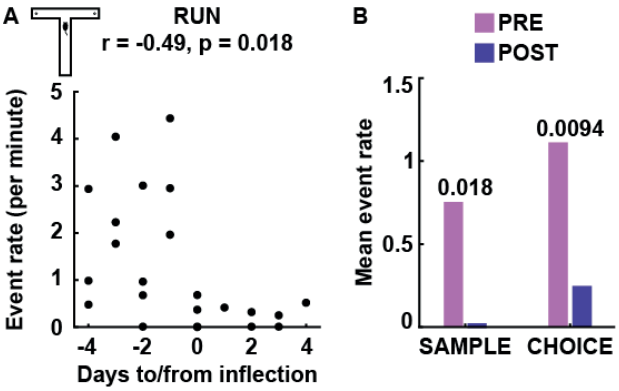
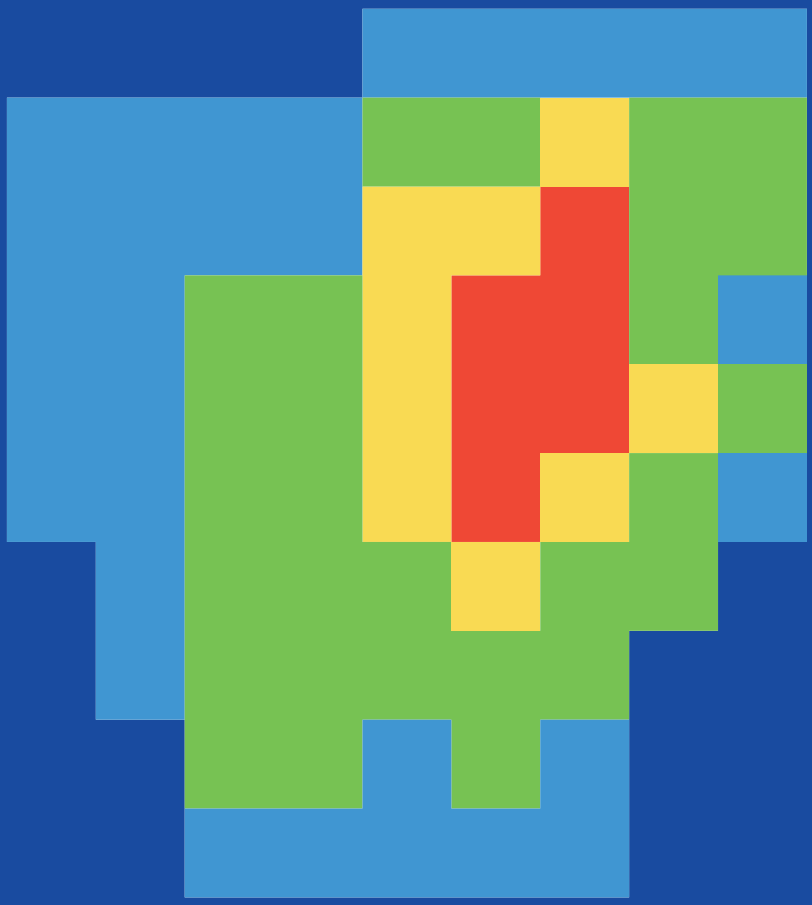


Figure S4.3. Incidence rates of replay events during Run periods of the task. (A) Session mean incidence rates (count/minute) of all replay events as a function of days to and from the inflection point. **(B)** Mean Run period incidence rates of Sample and Choice replay events separately.

Awake Sample					
	Pre mean (SD)	**Post mean (SD)**	**T-stat**	**df**	**p-value**
Stem	0.26 (0.18)	0.27 (0.12)	0.21	16	0.84
Approach	0.3 (0.2)	0.21 (0.08)	1.13	16	0.27
Arm	0.45 (0.24)	0.52 (0.17)	0.67	16	0.51
Stem x Approach			0.073	34	0.94
Stem x Arm			3.51	34	0.0013
Approach x Arm			3.56	34	0.0011
Awake Choice					
	Pre mean (SD)	**Post mean (SD)**	**T-stat**	**df**	**p-value**
Stem	0.33 (0.22)	0.34 (0.14)	0.12	21	0.9
Approach	0.22 (0.13)	0.24 (0.11)	0.31	21	0.76
Arm	0.45 (0.21)	0.42 (0.15)	0.33	21	0.75
Stem x Approach			2.26	44	0.029
Stem x Arm			1.96	44	0.057
Approach x Arm			4.64	44	<0.0001
Sleep Sample					
	Pre mean (SD)	**Post mean (SD)**	**T-stat**	**df**	**p-value**
Stem	0.22 (0.11)	0.33 (0.15)	2.04	22	0.053
Approach	0.32 (0.16)	0.25 (0.09)	1.35	22	0.19
Arm	0.46 (0.17)	0.42 (0.2)	0.51	22	0.62
Stem x Approach			0.64	47	0.53
Stem x Arm			3.86	47	0.00035
Approach x Arm			3.44	48	0.0012
Sleep Choice					
	Pre mean (SD)	**Post mean (SD)**	**T-stat**	**df**	**p-value**
Stem	0.37 (0.21)	0.29 (0.15)	1.16	27	0.26
Approach	0.2 (0.12)	0.25 (0.13)	1.2	27	0.24
Arm	0.44 (0.21)	0.46 (0.2)	0.3	27	0.77
Stem x Approach			2.58	57	0.013
Stem x Arm			2.24	57	0.029
Approach x Arm			5.021	58	<0.0001

Table S4.2. Summary statistics of the track portion reactivation analysis (see Figure 4.4).



Chapter 5

General discussion

5.1 Summary

Literature on episodic memory development primarily conducted with human children as participants is vast, but many unanswered questions remain. A critical area to be addressed is the link between developmental emergence of memory abilities and their underlying neurophysiological substrates. The field of neurophysiology of memory development is relatively new but it is a rapidly evolving field due to recent methodological advancements. The main goals of this thesis were to identify and highlight key questions in the field and attempt to directly relate the ontogeny of neural mechanisms thought to support memory to the emergence of memory capabilities in rodents.

In Chapter 2, we established the foundational theoretical framework of this thesis. In this chapter, we used Endel Tulving's seminal definition of episodic memory, where he describes this form of memory as memory for "*what* happens *where* and *when*" (E. Tulving, 1985; Tulving, 2002) and used this definition to review side-by-side studies on episodic memory ontogeny in different mammalian species. Directly comparing existing literature under the same framework provided the consistency necessary for knowledge synthesis. It allowed us to chart the gradual maturation of different constituent processes (i.e. encoding, recall/retention, 'what', 'where', when' memory) of memory across multiple species which allowed us to draw-up a cross-species developmental timeline for this critical cognitive capability. Namely, the human, non-human primate, and rodent literature all show a consistent developmental progression of item memory ("what") being the earliest to emerge, followed by location and spatial context ("where") memory. Upon emergence, "what-where" memory is relatively limited and only enables simple associations between a single item and location. It continues improving over a prolonged period of time as the abilities to make associations with multiple items and locations as well as integrating contextual information emerge. Even though the literature suggests that the ability to encode the temporal element ("when") of memory develops last, we found the evidence sparse and methodology inconsistent. We found a similar lack of research on the ontogeny of memory retention and retrieval, as well as a severe lack of direct relation between neurophysiological development and memory ontogeny. Therefore, in addition to unifying the literature from different species and methods under the same theoretical framework, Chapter 2 also offered a future prospective for what knowledge gaps remain to be addressed and a framework for addressing them systematically. In the subsequent chapters, we described research that addresses some of these knowledge gaps.

In Chapter 3, we for the first time directly related neuronal development to the emergence of memory capabilities. In our experiments, rat pups between the ages of 2-4 weeks were engaged in a delayed non-matching to place task testing spatial working memory (WM) task as we recorded their CA1 single units and LFP activity. Although this task is not an episodic memory task per se, we know that it relies on similar neural substrates as episodic memory capabilities. Hence, knowledge gained via the use of this task is likely to have implications for understanding episodic memory capabilities as well. Performance increased from below chance to above chance between two consecutive days in individual animals, and remained above chance from that point onward. This effect was not explained by experience. Relating neural activity to the periods prior to and after the inflection point of spatial WM performance, we found that place cell coding abruptly became task specific in tandem with memory emergence. Specifically, the ability of place cells to differentially represent the encoding and retrieval phases of the WM task predicted the animals' ability to carry out the task. We also analysed the local field potential (LFP) activity and found that the emergence of such memory encoding specificity is accompanied by an abrupt change in the temporal coordination of dominant CA1 inputs.

Chapter 4 focused on the development of population activity mechanisms underpinning memory. We investigated the functional development of sharp-wave ripples (SWR) and hippocampal reactivations thought to be critical for adult hippocampal memory. Sleep SWRs increased in duration as hippocampal memory emerged. Denser reactivations of the encoding phase of the task (i.e. more locations in the same amount of space) predicted spatial WM emergence. Further, we found that in tandem with WM emergence, hippocampal reactivations stopped occurring during the task and instead mostly occurred after the trial and preferentially depicted the reward location.

These findings provide valuable insight into the maturation of hippocampal function that may explain critical aspects of episodic memory ontogeny and advance our understanding of the neurophysiological bases of episodic memory capabilities across the lifespan.

5.2 Significance of findings

5.2.1 What cognitive and neurobiological changes underlie memory development?

One of the largest knowledge gaps in the field of memory development is relating the development neurophysiological processes to the unfoldment of cognitive abilities. Indeed, no rodent study so far has established a direct relation between neural development and emergence of memory capabilities. One of the aims of our work was to address this lack of empirical evidence. In Chapter 3, I presented the hippocampus-dependent spatial WM behavioural task used in all experiments described in Chapters 3-4 (Bevandić, Stella, et al., 2024). Correlating performance on the task to the age of our animals measured in post-natal days, we observed a gradual improvement from chance performance in the third week of life to significantly above chance performance in the fourth week of life. This result is consistent with existing literature using the same task (Green & Stanton, 1989b). However, considering individual animals' performance we noticed that the ability to carry out the task emerged abruptly, usually overnight, in individual animals. Furthermore, we observed considerable inter-animal variability with spatial WM emergence, with some animals displaying an inflection point as early as P19 whilst others did not reach this inflection point until P24. We captured this effect by fitting a sigmoid curve to each animal's daily performance data. This observation of abrupt memory emergence prompted several theoretical and methodological considerations.

The traditional approach to studying neural development in rodents is to measure the neural process of interest at different points early in life with the implicit assumption that memory development is a gradual process and that all animals' memory capabilities mature at the same rate. In our data, if we analysed performance for our entire cohort, we found maturation of spatial WM to be gradual. However, when we instead analysed individual animals' performance curves separately, we observed a developmental trend not captured by the cohort-wide analysis. The individual variability and abruptness of maturation has been reported on previously in the literature but not used to model individual neural maturation (Douglas et al., 1973a). This shows that important developmental dynamics (e.g. abrupt vs gradual maturation) may be overlooked if individual animal variability is not taken into account. In our experiments, the inflection point was consistently the better predictor of neural development when compared to post-natal day and experience using a GLM. In Chapter 3, our main result of the development of task phase remapping was highly significant as a function of the inflection point

($r = -0.5$, $p < 0.0001$). The same measurement of task phase remapping as a function of the post-natal day was still significant, but less so ($r = -0.22$, $p = 0.04$). By modelling individual animal developmental variability, we were able to capture the changes in neuronal function that may underlie memory development with increased precision and sensitivity than previously employed methods.

In terms of the specific neuronal developmental milestones, we observed spatial remapping from P17 in our experiment. Place cells are known to form place fields and exhibit spatial remapping from their emergence early in the third week of life (Langston et al., 2010a; Wills et al., 2010). The literature also suggests that place cells undergo gradual improvement in spatial precision and stability, an effect we also observed in our data. Thus, our findings are consistent with the research literature. We found another form of remapping – one where place cells alter their activity depending on which phase of the task an animal is carrying out (i.e. encoding vs retrieval) – matured during the age period we studied. Importantly, this task phase remapping seemed to emerge in tandem with the emergence of spatial WM; suggesting CA1 task phase coding may play a role in WM development. Furthermore, our results showed that the emergence of task phase remapping, and the concomitant narrowing of place fields we also observed, was better explained our inflection point analysis (which accounts for inter-animal variability) compared to our age-related analysis (that assumes WM development occurs at similar rates in different animals). What function might task phase remapping support? We interpret the emergence of task phase remapping as a form of encoding specificity. As discussed in Chapter 2, in humans, non-human primates and rodents, spatial what-where memory development is a protracted process. In Chapter 2, we demonstrated that encoding specificity emerges gradually. For example, experiments with rodents and non-human primates show that early in life animals can encode single objects or spatial locations in an environment, but the ability to encode more complex relations and the context within which they occur matures relatively late. This ability to distinguish distinct memories formed from overlapping sets of associations might be an important milestone in episodic memory development. We conjecture that encoding specificity may be supported by mechanisms such as task phase remapping, where place cells integrate multi-modal input in the service of orthogonalizing representations for related but distinct environments, and the reason why aspects of memory capabilities only emerge later in life, is because this neurophysiological function develops late.

Literature indicates that improvement in place cell coding specificity might be reflective of the entorhinal cortex (EC) maturation (Bevandić, Chareyron, et al.,

2024; Langston et al., 2010a; Wills et al., 2010). In Chapter 3, we also investigated this possibility by studying changes in hippocampal inputs in relation to memory development. Different phases of the CA1 hippocampal theta cycle as well as different gamma-band oscillations (slow vs medium gamma) have been related to ECIII and CA3 input (Guardamagna et al., 2023; Hasselmo et al., 2002; Siegle & Wilson, 2014). When ECIII exerts stronger control over CA1 activity, CA1 cells are known to fire at earlier phases of theta-band oscillations and medium gamma is stronger. On the other hand, when CA3 input dominates, CA1 cells fire later in the theta cycle (near the trough) and slow gamma oscillations become stronger. Importantly, the two inputs are also thought to support complementary mnemonic processes – with CA3 input thought to support memory retrieval and ECIII input thought to support memory encoding (Hasselmo et al., 2002; Manns et al., 2007). In our spatial WM task, we found memory emergence was associated with a divergence in the preferred theta phase of CA1 spikes for the two task phases. Namely, as the animals started to be able to do the task, Sample (i.e. encoding) task phases were associated with significantly earlier preferred theta phase relative to Choice (i.e. retrieval) task phases. Furthermore, we observed the ratio between slow and medium gamma coupling to theta-band oscillations favoured neither gamma band prior to WM emergence. However, as WM matured, the ratio tilted in opposite directions for the two task phases – with medium gamma becoming stronger for Sample task phases and slow gamma dominating during Choice task phases. Thus, these findings suggest that WM maturity may depend on the development of CA1 sub-circuit temporal orchestration. We conjecture that the development of place cells remapping and CA1 input segregation are related. As CA3 or ECIII input diverge in temporal coding and begin to dominate during one of the two task phases, the spatial coding of place cells begins to differ between distinct task phases. In other words, the temporal segregation may be the mechanism that leads to task phase remapping. Thus, development of mature CA1 sub-circuits and task specific representations may be intrinsically linked and together they support the emergence of encoding specificity; a hallmark of episodic memory ontogenesis.

Sharp-wave ripples (SWRs) and hippocampal reactivations are thought to be critical to adult memory function. Specifically, they are thought to support the commission of new memories to long-term storage as well as planning (Bevandić, Chareyron, et al., 2024; Buzsáki et al., 1992; Ólafsdóttir et al., 2018; Wilson & McNaughton, 1994). As the memory task we used relies on planning, we sought to investigate if WM maturity could be explained by changes SWRs and/or reactivations. Similar to chapter, 3, our analyses produced task-phase specific results in line with findings from Chapter 3. As spatial WM matured, reactivation events depicting the encoding

(sample) phase of the task reactivated more unique locations. The length of the reactivated segment of the track did not change with memory maturation, however. Therefore, memory maturation was predicted by increased specificity of hippocampal reactivations (i.e., same space in more detail). Crucially, this effect was limited to the encoding phases of the task. Another memory development-related finding we observed, was that SWRs increased in duration as WM matured, suggesting (working) memory development may relate to the development of longer SWRs. Although these aspects of SWRs and reactivations have not been studied systematically, recently Berners-Lee et al. (2022) showed adult reactivation become longer in duration and contain more detailed depictions of experienced places as animals become more fluent with a task; akin to our results. Further, Fernández-Ruiz et al. (2019) causally linked increased SWR duration to improved improved performance on a WM task. Thus, specificity of reactivations as well as their duration may be critical aspects of hippocampal function that may mediate its contribution to mature memory.

5.2.2 What does ontogeny teach us about the neurophysiological bases of adult memory?

Most of our understanding of the hippocampal network and mechanisms is based on studies on adult brains. A common way to determine the function of some mechanism in adult animals is to lesion/inactivate the region of interest and measure its impact. Ontogeny is a natural parallel to this approach as we can observe the impact the emergence of a given neurophysiological mechanisms has on the emergence of behavioural capability. Further, identifying specific hippocampal representations/ circuit mechanisms that underlie individual components of mature memory (e.g. encoding vs retrieval) is a formidable challenge in adult animals, as these processes likely engage overlapping circuit processes. Thus, our developmental analysis may not only offer insight into the critical neurophysiological milestones for memory development, but they may also clarify the link between specific neural processes and individual aspects of mature memory capability.

Namely, we found that spatial remapping alone is not sufficient for spatial WM performance. The specific ability of place cells to remap between distinct task-phases predicted memory emergence. This finding highlights the role of non-spatial coding in the hippocampal function. It has been previously established that the hippocampus encodes more than spatial variables (Anderson & Jeffery, 2003; Bostock et al., 1991; Fyhn et al., 2007; Wood et al., 2000). In fact, our results corroborate those of Griffin et al. (2007). However, by demonstrating that task-phase remapping might be necessary for spatial memory emergence, we emphasise that

the critical role of non-spatial encoding in the hippocampus for mature memory. Furthermore, our data from Chapter 3 also gives support to influential theories suggesting that CA3 and ECIII input to CA1 support distinct memory processes (Hasselmo et al., 2002). These theories have already been corroborated with causal evidence (Siegle & Wilson, 2014). However, our data suggests that the dynamic switching of CA1 inputs to selectively promote encoding or retrieval might not only improve encoding and retrieval but be a prerequisite for WM in general.

Multiple adult studies, suggest awake replay supports planning (Diba & Buzsáki, 2007; Pfeiffer & Foster, 2013a; Singer et al., 2013b). However, the empirical evidence for this theory is mixed as multiple studies failed to relate awake replay to immediate behaviour (Davidson et al., 2009; Gupta et al., 2010; Karlsson & Frank, 2009a). As our WM task relies on planning, we reasoned that if replay did support planning one should expect to see developmental changes in replay that relate to WM capability. For example, one might expect the rate of replay to increase at time points during the task when planning is most likely to occur (e.g. between an encoding and a choice trial, or while running on the track). However, our results indicate the opposite to be true. Once the ability to carry out the task emerged, the number of awake reactivation events that occurred on the track significantly reduced and even completely stopped occurring in most sessions. This effect could be partially explained by the animals rarely pausing after they develop the ability to carry out the task, as reactivations mostly occur when the animals are stationary. However, each trial has two interval periods during which the animals are mostly stationary. The delay period between the sample and choice would represent the most efficient moment to plan a future trajectory. Whereas any replay during the inter-trial interval after the animal receives the reward and before the next randomised sample run begins has no bearing on future trajectories. We observed no change in the number of reactivations during the delay period, and a significant post-maturation increase in inter-trial interval reactivations. Furthermore, this developmental pattern of reduced reactivations during the trial and increased reactivations after the trial was present in both reactivations representing encoding and retrieval phases of the task. As noted in the preceding section, we did observe some developmental trends for replay (e.g. increased reactivation specificity and SWR duration). However, whilst reactivation specificity increased in both awake and sleep periods, SWRs increased in duration only during sleep. As such, the link between these developmental effects and planning is unclear. Taken together, our results on the ontogeny of hippocampal reactivations do not provide support to the planning hypothesis for replay.

5.3 Caveats and future outlook

The work described in this thesis provides evidence that relating neural development directly to memory maturation provides valuable insight into the neurophysiological basis of memory ontogeny. This work highlights the need to study the link between neurophysiology and cognition directly, as many of the findings we observed we would not have obtained without using such a direct approach. As such, we encourage the developmental neuroscience community to study neuronal development more often in direct relation to cognitive development.

One of the main limitations of our current project was the cell yield on individual sessions. We collected most of the data using 32-channel tetrode bundle microdrives. Although we attained markedly higher cell yields using 64-channel microdrives in a couple of animals, our session cell yield across the dataset was too low to carry out extensive replay analysis. Furthermore, dividing our data into the four different run types was necessary to address task-related modulation of neural activity, which effectively further lowered the cell yield (e.g. if a place cell was not active in some run types). Hippocampal replay analyses that measure the reactivation of place cell sequences are known to require high cell counts. For this reason, we had to use a simpler approach to the reactivation analyses which mean we could not directly compare our reactivation results to the few studies on hippocampal replay development published (Farooq & Dragoi, 2019; Muessig et al., 2019b). Hopefully future studies may address this point by employing state-of-the-art electrophysiological techniques such as Neuropixels probes.

Despite devoting Chapter 2 to reviewing the literature on the development of episodic(-like) memory, in our experiments we used a spatial WM task. Nevertheless, neural circuits supporting WM and episodic memory, particularly in the spatial domain, are known to greatly overlap (Guderian et al., 2015). As such, this task could be used to chart the maturation of the relevant neurophysiological milestones underlying episodic memory. Indeed, the main goal of this project was to investigate development, and this task provided clear individual inflection points which provided a powerful way to capture neurodevelopemental changes underlying memory development. In Chapter 2 we described a number of memory tasks that may more precisely measure episodic-like memory development, which we hope future studies will employ.

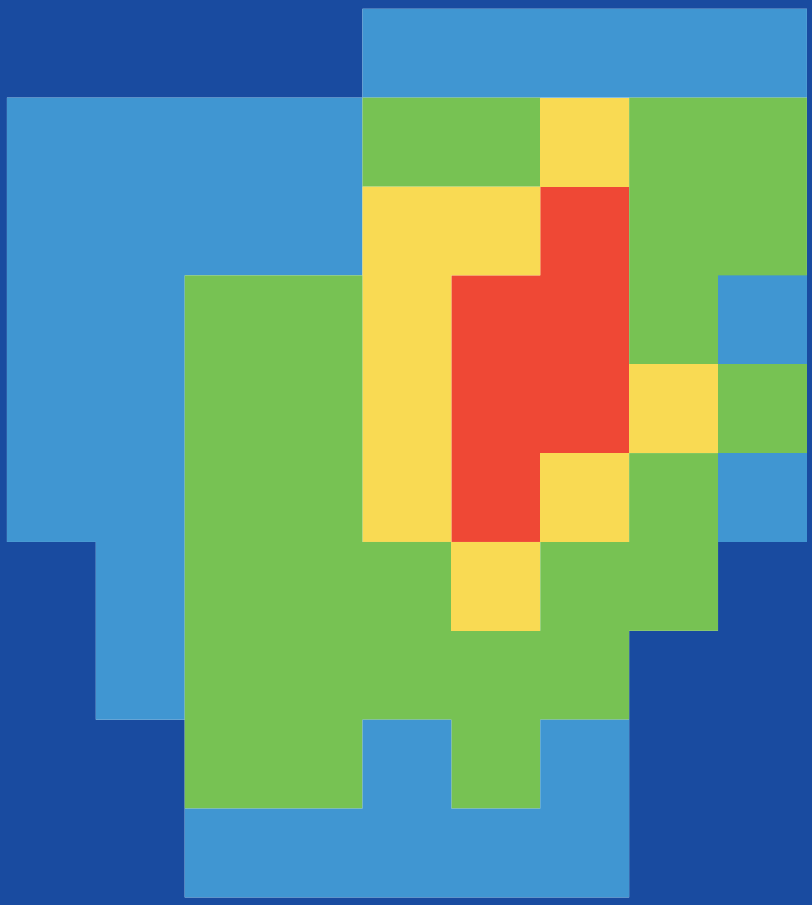
Finally, our results were partially limited by our choice of electrophysiological methods. Since this was the first study combining freely moving in-vivo electrophysiology with daily behavioural tests in rat pups, we opted for a method

that is well established in adults (e.g. tetrode recording). However, the limitation of tetrodes is the lack of access to laminar information, such as which sublayer of CA1 we were recording from and we could only assume that our tetrodes were closest to the pyramidal layer. To investigate sub-circuit maturity (e.g. ECIII vs CA3 input) such laminar information is crucial. Although we were able to address this topic indirectly, by measuring theta-gamma coupling, there were many analyses we were not able to perform because of this limitation (e.g. measuring strength of ECIII and CA3 input). Future studies using, for example, Neuropixels probes or independently moveable tetrodes which can target different regions of the hippocampal formation would overcome this limitation.

5.4 Concluding remarks

Despite the lack of explicit connections and collaboration between different research lines, our understanding of the cognitive development underlying episodic-like memory emergence is reasonably detailed. A cohesive narrative of memory emergence can be drawn from the existing literature, as presented in this thesis. However, this knowledge synthesis highlights that significant caveats still remain unaddressed. We have only recently started gaining first insights into the neurodevelopmental milestones that might underlie memory maturation. For example, no study prior to work presented in this thesis has directly linked cognitive development to neurophysiological development.

Understanding memory development has potential implications beyond the curiosities of its emergence. Every developing brain is a natural display of prerequisites for healthy memory function. Therefore, memory development research complements adult memory research and might even offer the causal insight not easily achievable studying the mature hippocampus. Beyond theory, discovering the essential developmental milestones could identify key target mechanisms and physiology to diagnose or treat in clinical practice. It is my goal and hope that both theoretical and experimental work presented in this thesis can be seen as a starting point in filling these essential knowledge gaps.



Appendix

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Donders Graduate School for Cognitive Neuroscience

For a successful research institute, it is vital to train the next generation of young scientists. To achieve this goal, the Donders Institute for Brian, Cognition and Behaviour established the Donders Graduate School for Cognitive Neuroscience (DGCN), which was officially recognised as a national graduate school in 2009.

The Graduate School covers training at both Master's and PhD level and provides an excellent educational context fully aligned with the research programme of the Donders Institute.

The school successfully attracts highly talented national and international students in biology, physics, psycholinguistics, psychology, behavioral science, medicine and related disciplines. Selective admission and assessment centers guarantee the enrolment of the best and most motivated students.

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For more information on the DGCN as well as past and upcoming defenses please visit: https://www.ru.nl/donders/graduate-school/phd/ (QR code related).

Research Data Management

The research presented in this thesis has been carried out under the institute research data management policy of the Donders Institute for Brain, Cognition and Behaviour (as of July 2023, https://www.ru.nl/rdm/vm/policy-documents and https://www.ru.nl/en/donders-institute/research/open-science). The research has followed all applicable laws and ethical guidelines. Research Data Management was performed according to the FAIR principles.

Ethical approval

This thesis describes animal experiments, which were conducted by certified animal experimenters in accordance with the European, Dutch and local regulations on the basis of the DEC Project 2018-0038. The local Animal Welfare Body has approved the protocols for the present project 2018-0038-001, 2018-0038-002, 2018-0038-003.

Findability and accessibility

The data for each experimental chapter can be found published on the Radboud Repository as Data Sharing Collections (DSC). All data archived as a DSC remains available for at least 10 years after termination of the study. All data have been published under the CC0-1.0 use agreement.

Chapter 3 data

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Chapter 4 data

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English summary

Episodic memory, also known as 'what-where-when' memory, is the ability to recall autobiographical events within their wider context. However, this form of memory is not present at birth but only emerges gradually throughout childhood. Its delayed and protracted maturation is understood to be caused by equally protracted development of neural mechanisms supporting episodic memory. However, memory development remains a relatively understudied topic of memory research with little consensus on the processes underlying memory emergence. The goal of this thesis was to establish a common framework for synthesis of existing knowledge as well as identification of open questions and best practices. In addition, we also aimed to address one of the key knowledge gaps, namely, directly relating neural and cognitive development for the first time.

In Chapter 2, we provide a comprehensive review of the literature across human, non-human primate, and rodent memory development research. Each species literature provides a unique insight into cognitive, anatomical or functional development, but collaboration and knowledge exchange between different lines of research was lacking. We demonstrated that memory maturation tends to follow a comparable timeline in all three species. Moreover, memory commonly gradually matures from simpler (e.g. a single object in a certain position) towards more complex associations (e.g. multiple objects in a specific order, each in a different environment). However, we also identified several crucial knowledge gaps, amongst other the lack of data directly relating neural development to cognitive development and addressing the role of sleep in memory development.

In Chapter 3, we for the first time directly related the development memory abilities to the development of mechanisms known to support memory. We chronically recorded CA1 single-unit and population (LFP) activity as early post-natal rat pups developed the ability to carry out a spatial working memory (WM) task that relies on much of the same neurobiology as episodic-like memory. Importantly, spatial WM matures abruptly, usually overnight, and the day of its emergence can vary greatly between different animals. We used a task that allowed us to identify the individual inflection point of spatial MW abilities for each animal, and use the individual developmental trajectories to relate memory emergence to changes in neural activity. We confirmed that place cells are present and can remap prior to memory emergence, but showed that their sudden ability to remap to distinct behaviourally relevant task phases emerges together with spatial WM. Place cells also narrowed their place fields with development, but this fact alone did not

account for the maturation of task-phase remapping. Instead, we showed that at the same time the major CA1 inputs, distinctly related to encoding and retrieval processes, begin dynamically changing their balance to match task requirements.

In Chapter 4, we investigated the prominent population mechanisms that support adult memory consolidation and maintenance. This data was collected from the same animals as they performed the task and slept immediately after performing the task. We showed that spatial WM emergence is accompanied by increasingly long sleep sharp-wave ripples (SWRs). We also investigated hippocampal reactivations that occur during SWRs, and found that spatial WM emergence correlates with reactivations of more spatial locations. However, the spatial extent of the track reactivated did not increase, indicating that the reactivations were becoming denser and more fine-grained. This effect was also task phase-dependent, and only observed in the encoding task phase that drove task-phase remapping in Chapter 3. Both prior and after spatial WM emergence, locations closer to the reward locations were reactivated more than the rest of the track. Similar results in the literature have led to the suggestion that reactivations during awake behaviour might serve a planning role. We tested this hypothesis by investigating whether reactivations occur when the animal needs to make an immediate plan during the task or whether they occur after the trial when no plan can be made. When spatial WM matured, reactivations during the task nearly completely ceased, but they increasingly occurred after the trial. Therefore, we showed that reactivations did not serve the function of planning in our task, but likely reflected the consolidation and maintenance of the newly emergent ability of place cells to distinctly represent different task phases.

In conclusion, this thesis provided a comprehensive overview of memory development and established previously missing connections as well as overlooked caveats and knowledge gaps. It also addressed the largest knowledge gaps by providing the first data directly relating neural and cognitive development. This work and findings may help improve the quality of future research on the topic or inspire new and improved theories of episodic memory development.

Dutch summary

Het episodische geheugen, ook bekend als 'wat-waar-wanneer' geheugen, is het vermogen om autobiografische gebeurtenissen in hun bredere context terug te halen. Deze vorm van geheugen is echter niet aanwezig bij de geboorte, maar komt pas geleidelijk tot ontwikkeling tijdens de kindertijd. De vertraagde en langdurige ontwikkeling wordt veroorzaakt door de eveneens vertraagde ontwikkeling van neurale mechanismen die het episodisch geheugen ondersteunen. Echter, geheugenontwikkeling blijft een relatief onderbelicht onderwerp van geheugenonderzoek met weinig consensus over de processen die ten grondslag liggen aan het ontstaan van geheugen. Het doel van deze dissertatie was om een gemeenschappelijk raamwerk op te zetten voor de synthese van bestaande kennis en het identificeren van open vragen en best practices. Daarnaast wilden we ook een van de belangrijkste kennishiaten aanpakken, namelijk het voor het eerst direct in verband brengen van neurale en cognitieve ontwikkeling.

In hoofdstuk 2 geven we een uitgebreid overzicht van de literatuur over onderzoek naar geheugenontwikkeling bij mensen, niet-menselijke primaten en knaagdieren. De literatuur van elke soort biedt een uniek inzicht in cognitieve, anatomische of functionele ontwikkeling, maar samenwerking en kennisuitwisseling tussen verschillende onderzoekslijnen ontbrak. Wij toonden aan dat geheugenontwikkeling bij alle drie de soorten een vergelijkbare tijdlijn volgt. Bovendien rijpt het geheugen gewoonlijk geleidelijk van eenvoudiger (bijv. een enkel object in een bepaalde positie) naar complexere associaties (bijv. meerdere objecten in een specifieke volgorde, elk in een andere ruimte). We hebben echter ook een aantal cruciale hiaten in vakgebied kennis geïdentificeerd, waaronder het gebrek aan gegevens die de neurale ontwikkeling direct in verband brengen met de cognitieve ontwikkeling en die de rol van slaap in de ontwikkeling van het geheugen onderzoeken.

In hoofdstuk 3 hebben we voor het eerst een direct verband gelegd tussen de ontwikkeling van geheugenvaardigheden en de ontwikkeling van mechanismen waarvan bekend is dat ze het geheugen ondersteunen. We verzemelden chronisch CA1 enkele-cel en populatie (eng., LFP) activiteit terwijl vroege postnatale rattenjongen het vermogen ontwikkelden om een ruimtelijke werkgeheugentaak (eng., WM) uit te voeren die grotendeels berust op dezelfde neurobiologie als het episodisch geheugen. Belangrijk is dat ruimtelijk werkgeheugen abrupt tot wasdom komt, meestal van de ene op de andere dag, en de dag waarop het tot wasdom komt kan sterk variëren tussen verschillende dieren. We gebruikten een taak die ons in staat stelde om het individuele buigpunt van ruimtelijke WM vaardigheden voor elk dier te

identificeren en de individuele ontwikkelingstrajecten te gebruiken om het ontstaan van het geheugen te relateren aan veranderingen in neurale activiteit. We bevestigden dat plaatscellen aanwezig zijn en zich kunnen herschikken voorafgaand aan het ontstaan van het geheugen, maar toonden aan dat hun plotselinge vermogen om zich te herschikken naar verschillende gedragsrelevante taakfasen ontstaat samen met ruimtelijk WM. Plaatscellen vernauwden ook hun plaatsvelden tijdens de ontwikkeling, maar dit feit alleen was niet verantwoordelijk voor de rijping van taak-fase remapping. In plaats daarvan toonden we aan dat op hetzelfde moment de belangrijkste CA1 inputs, die duidelijk gerelateerd zijn aan coderings- en terughaalprocessen, dynamisch hun balans beginnen te veranderen om te voldoen aan de taakvereisten.

In Hoofdstuk 4 onderzochten we de prominente populatiemechanismen die geheugenconsolidatie en -onderhoud bij volwassenen ondersteunen. Deze gegevens werden verzameld bij dezelfde dieren terwijl ze de taak uitvoerden en sliepen direct na het uitvoeren van de taak. We toonden aan dat ruimtelijke WM opkomst gepaard gaat met steeds langere slaap sharp-wave ripples (SWRs). We onderzochten ook hippocampus reactivaties die optreden tijdens SWRs, en vonden dat ruimtelijke WM opkomst correleert met reactivaties van meer ruimtelijke locaties. De ruimtelijke omvang van het gereactiveerde spoor nam echter niet toe, wat aangeeft dat de reactiveringen dichter en fijnkorreliger werden. Dit effect was ook taakfase-afhankelijk en werd alleen waargenomen in de codering taakfase die taakfase-remapping in Hoofdstuk 3 aanstuurde. Zowel voor als na het ontstaan van ruimtelijke WM werden locaties dichter bij de beloningslocaties meer gereactiveerd dan de rest van het pad. Vergelijkbare resultaten in de literatuur hebben geleid tot de suggestie dat reactiveringen tijdens wakker gedrag een planningsfunctie zouden kunnen hebben. We testten deze hypothese door te onderzoeken of reactiveringen optreden wanneer het dier een onmiddellijk plan moet maken tijdens de taak of dat ze optreden na de trial wanneer er geen plan gemaakt kan worden. Toen ruimtelijk WM volwassen werd, hielden reactiveringen tijdens de taak bijna volledig op, maar ze traden steeds vaker op na de trial. Dus we aantoonden dat reactiveringen niet de functie van planning in onze taak dienden, maar waarschijnlijk consolidatie en het onderhoud van het nieuw ontstane vermogen van plaatscellen weerspiegelden om verschillende taakfasen te onderscheiden.

Concluderend, dit proefschrift gaf een uitgebreid overzicht van geheugen-ontwikkeling en legde eerder ontbrekende verbanden en over het hoofd geziene voorbehouden en kennishiaten bloot. Het heeft ook de grootste kennislacunes

aangepakt door de eerste gegevens te leveren die neurale en cognitieve ontwikkeling direct met elkaar in verband brengen. Dit werk en deze bevindingen kunnen bijdragen aan het verbeteren van de kwaliteit van toekomstig onderzoek over dit onderwerp of inspireren tot nieuwe en verbeterde theorieën over de ontwikkeling van het episodisch geheugen.

Curriculum vitae

Juraj was born in Rijeka, Croatia. He studied Analytic Philosophy and Logic, and English Language and Literature at the University of Rijeka and Karl-Franzens Universität Graz. He graduated from his Bachelor's programme with a thesis "Objections to McGinn's Cognitive Closure Argument" supervised by Prof Dr Luca Malatesti. Increasingly focusing his academic interests on the philosophy of mind and science, and inspired by Immanuel Kant's intuition of space, Juraj decided to continue his education in neuroscience.

He attended the Research Master's programme in Cognitive and Clinical Neuroscience at Maastricht University. During his Master's studies, Juraj further developed his interest in the hippocampus and memory in the research group of Prof Dr Peter de Weerd. After a 9-month research internship in the lab of Prof Dr Lisa Genzel where he built and piloted the Hex Maze at Radboud University and Donders Institute in Nijmegen, Juraj graduated with his thesis "Novel Rat HexMaze and Hippocampal Independence of Schema Updates in the Mouse HexMaze: A Tale of Two Tails".

After a productive and exciting year in Nijmegen, Juraj remained at Radboud and Donders to pursue his PhD in the freshly established lab of Dr Freyja Ólafsdóttir. Their work resulted in three high-profile publications, numerous conference posters, and a doctoral thesis titled "The ontogeny of hippocampal memory: Bridging behavioural and neuronal development". With this, Juraj has achieved his dream of studying place cells at the very frontiers of our understanding, and has subsequently departed academia to pursue new goals and challenges.

List of publications

1. Bevandić, J., Genzel, L., & Ólafsdóttir, H. F. (2021). Shining a light on hippocampal remapping. Neuron, 109(6), 913-915, doi: 10.1016/j.neuron.2021.02.020

2. Bevandić, J., Chareyron, L. J., Bachevalier, J., Cacucci, F., Genzel, L., Newcombe, N. S., Vargha-Khadem, F., & Ólafsdóttir, H. F. (2024). Episodic memory development: Bridging animal and human research. Neuron, 112(7), 1060-1080, doi: 10.1016/j.neuron.2024.01.020

3. Bevandić, J., Stella, F., & Ólafsdóttir, H. F. (2024). Parallel maturation of rodent hippocampal memory and CA1 task representations. Current Biology, doi: 10.1016/j.cub.2024.08.048

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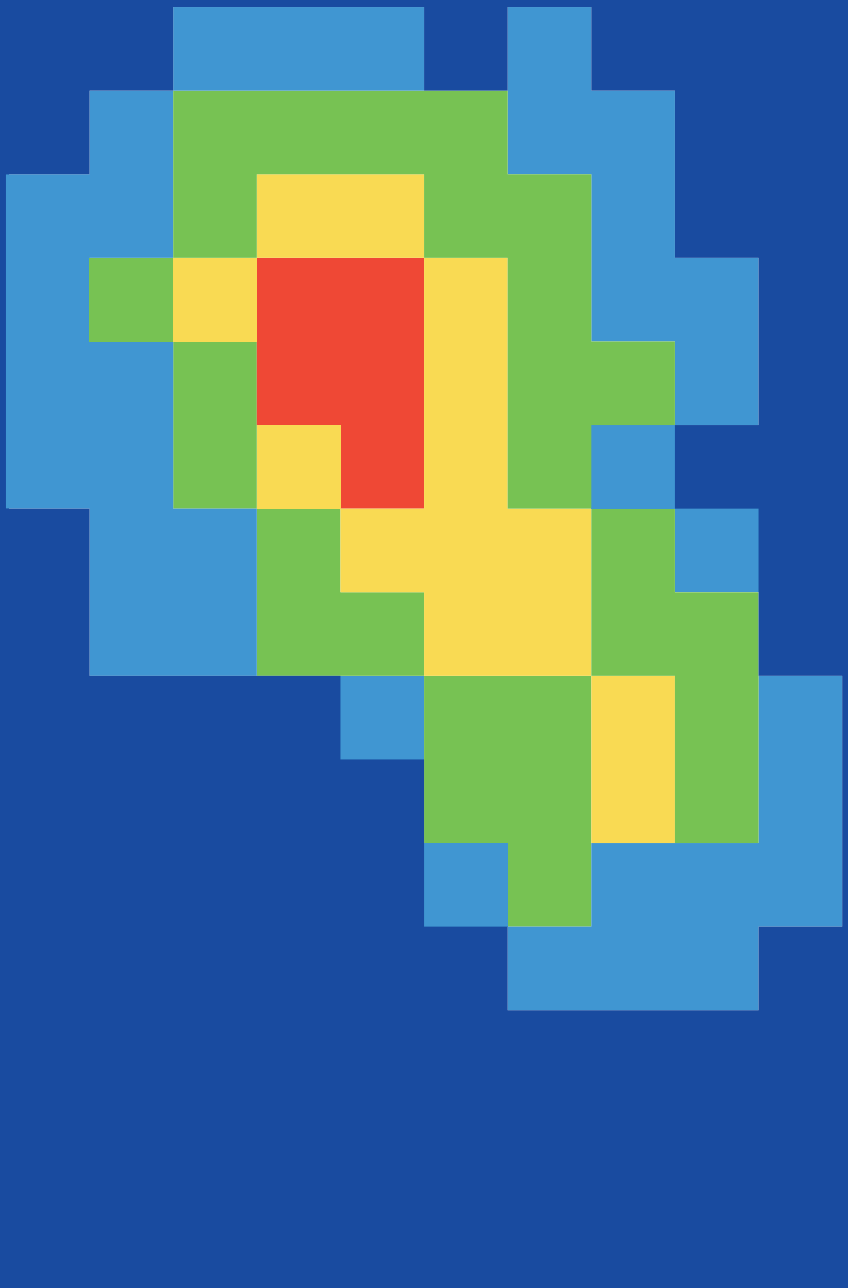

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