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Review

Construction and disruption of spatial memory networks during development

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Spatial memory, the aspect of memory involving encoding and retrieval of information regarding one's environment and spatial orientation, is a complex biological function incorporating multiple neuronal networks. Hippocampus-dependent spatial memory is not innate and emerges during development in both humans and rodents. In children, nonhippocampal dependent egocentric (self-to-object) memory develops before hippocampal-dependent allocentric (object-to-object) memory. The onset of allocentric spatial memory abilities in children around 22 mo of age occurs at an age-equivalent time in rodents when spatially tuned grid and place cells arise from patterned activity propagating through the entorhinal–hippocampal circuit. Neuronal activity, often driven by specific sensory signals, is critical for the normal maturation of brain circuits This patterned activity fine-tunes synaptic connectivity of the network and drives the emergence of specific firing necessary for spatial memory. Whereas normal activity patterns are required for circuit maturation, aberrant neuronal activity during development can have major adverse consequences, disrupting the development of spatial memory. Seizures during infancy, involving massive bursts of synchronized network activity, result in impaired spatial memory when animals are tested as adolescents or adults. This impaired spatial memory is accompanied by alterations in spatial and temporal coding of place cells. The molecular mechanisms by which early-life seizures lead to disruptions at the cellular and network levels are now becoming better understood, and provide a target for intervention, potentially leading to improved cognitive outcome in individuals experiencing early-life seizures.

Spatial memory networks encompass precisely interacting cell populations within the hippocampal formation and interacting cortical regions. The development of these circuits involves activity- and sensory-signal-dependent and independent components. Orchestrated development of these networks is crucial for memory function throughout life: conversely, disruptions of memory network development arise at molecular, cellular and circuit levels with major, clinically relevant cognitive deficits. Our understanding of how and when these different memory systems emerge during the course of human development has been expanding rapidly. In this review, the developmentally regulated construction of human and rodent functional memory networks is discussed. This is followed by a discussion of how insult-related disruption of this development can inform the fundamental principles of memory as well as clarify disease mechanisms.

Spatial memory development in humans

Memory is a complex biological function incorporating multiple neuronal networks. Likewise, the taxonomy of memory is convoluted. Current thought is that there are at least two major kinds of memory, declarative (or explicit), memory and procedural, often referred to as implicit or nondeclarative memory (Zola-Morgan et al. 1983; Squire 1986; Squire et al. 1990). Declarative memory refers to memory that can be declared in some way and includes the conscious recollection of facts and events (Squire and Zola-Morgan 1985, 1988; Squire et al. 1990; Zola-Morgan and Squire 1993). Within the declarative memory domain there is a further distinction between semantic and episodic memory. Semantic memory refers to memory for factual information, while episodic memory refers to memory of a personal experience, that is memory of "what-where-when." Procedural memory refers to information that is reflected in behavior but that cannot be consciously recalled. For example, highly practiced motor behaviors such as driving a car or playing the piano are examples of procedural memory skills.

Spatial memory is the aspect of memory responsible for encoding and retrieval of information regarding one's environment and spatial orientation. In rodents, spatial memory is considered equivalent to declarative memory in humans (Bunsey and Eichenbaum 1996; Crystal and Smith 2014; Eichenbaum and Cohen 2014). Spatial coding can be allocentric (object-to-object) where the location of one object is defined relative to the location of other objects or egocentric (self-to-object) where the location of objects in space is relative to the body axes of the self. Allocentric, semantic, and episodic memory are dependent on the hippocampus, entorhinal cortex (EC), and surrounding structures (Scoville and Milner 1957; Zola-Morgan et al. 1986; Hoscheidt et al. 2010; Banta Lavenex et al. 2014) whereas egocentric navigation involves the dorsal striatum and connected structures. The latter system encodes routes and integrated paths and, when overlearned, becomes procedural memory (Ribordy et al. 2017).

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Declarative memory is not an innate faculty and emerges during early childhood. Infantile amnesia, first described by Sigmund Freud in the late nineteenth century (for review, see Josselyn and Frankland 2012), is the term used to describe the fact that adults have essentially no explicit memories from the first 2–3 yr of life, whereas childhood amnesia describes the observation that adults have fewer explicit memories from 3 to 7 yr of age than would be expected based on normal forgetting alone. The phenomena of infantile and childhood amnesia suggest that hippocampus-dependent declarative memory may not be evident during the first few years of life. However, it is important to note that by the age of 6 mo, infants have acquired at least some rudimentary memory skills (Rovee-Collier et al. 1980, 1985; Hayne et al. 1987, 1991; Rovee-Collier and Hayne 1987; Hayne and Rovee-Collier 1995; Collie and Hayne 1999; Hayne and Herbert 2004). For example, in the visual paired comparison task (also referred to as a habituation and novelty-preference paradigm), an infant will spend less time looking at a familiar object relative to a novel object. Notably, this task is probably not hippocampus-dependent and occurs because of modifications of a perceptual-cognitive process (i.e., priming processes) without any explicit knowledge or reference to the study context (Mullally and Maguire 2014). Likewise, although infants as young as 3 mo can be taught to activate a crib mobile by means of operant foot kicks (Rovee-Collier et al. 1980), this test is considered to be nondeclarative in nature (Bauer 2008; Mullally and Maguire 2014). It has been suggested that this operant task most likely depends on the cerebellum and brain stem, which mature prior to the hippocampus and which likely support a primitive, nondeclarative memory system (Bauer 2008; Mullally and Maguire 2014).

Egocentric capabilities emerge prior to allocentric ones and tend to dominate the infant's spatial world for at least the first 6 mo of life (Lavenex and Banta 2013). The use of cues or landmarks to remember spatial locations begins to appear at the end of the first year of life (Bushnell et al. 1995; Lew et al. 2000). Path integration, often referred to as dead reckoning, becomes apparent in children during the second year of life (Bremner et al. 1994). Path integration is the process of continuous integration of idiothetic cues, such as vestibular, proprioception, odors, motor efference and optic flow (information from the visual system signaling how fast the visual world is moving past the eyes) that allows for successful navigation to a specific goal (Wylie et al. 1999; Wallace et al. 2002a,b; Sjolund et al. 2018). There is considerable evidence that egocentric spatial memory is not dependent on the hippocampus (Vorhees and Williams 2014). Individuals with hippocampal and EC damage do as well on a path integration task as individuals with normal hippocampi and EC (Shrager et al. 2008).

In contrast, elegant experiments support the notion that allocentric spatial memory abilities in children emerge around 22 mo of age (Newcombe et al. 2007; Ribordy et al. 2013, 2017). Specifically, in a series of experiments by Ribordy et al. (2013, 2017), children were asked to find rewards hidden beneath cups in an open-field arena, over repeated trials. In the experiment children were asked to locate candy hidden under one of four inverted cups placed in an arena that was surrounded on three sides by opaque curtains, thus preventing the child from using aligned or adjacent objects as uncontrolled visual guidance cues. The child entered the arena through four separate entry/exit points which precluded the child from using egocentric cues. In the local cue condition, a red cup concealed the candy, thus allowing the investigators to assess whether the child could use a controlled visual guidance cue (nonhippocampus dependent) to find the candy. Since the local cue, the red cup, was readily visible to the child the hippocampus is not needed to remember distant cues. In the allocentric, hippocampus-dependent task, all four cups were identical, and children had to use an allocentric spatial representation of the environment to remember the rewarded cup's location. Whereas 80% of the children between 20 and 24 mo found the correct cup when given a local cue, only 30% of the children could find the candy in the allocentric spatial condition, in the absence of the local cue. In children 25–39 mo of age, 100% found the candy in the local cue condition, and 84% in the allocentric condition. These findings support work by Newcombe et al. (2007) showing that children 22 mo of age and older benefited from the presence of distal visual objects when searching for objects buried in a sandbox, whereas younger children did not. The developmental timing of allocentric memory in children is further supported by studies by Hayne and Imuta (2011). These authors developed a hide-and-seek paradigm and assessed young children's (3- and 4-yr-olds) ability to recollect the "what-where-when" of a hiding event.

Together, the above studies suggest that the development of episodic memory is protracted throughout early and middle childhood, although rudimentary episodic memory skills do appear to be in place by the age of 3 yr. There is increasing evidence that the ability to retain, as opposed to form episodic memories may be the aspect of this form of memory that develops later. While both 3- and 4-yr-old children form episodic memories, 3-yr-old children fail to retain those memories following a delay (Scarf et al. 2013). In contrast, 4-yr-old children retained episodic memories over delays of a day and a week. These data suggest that childhood amnesia might be a result of an inability to retain, rather than to form, an episodic memory.

Allocentric spatial learning and memory emerges at a time when the hippocampus is structurally and functionally approaching maturity. While hippocampal volume approximates that of the adult by 10 postnatal months (Kretschmann et al. 1986), neuronal differentiation and synaptogenesis in the hippocampus do not reach adult levels until 3–5 yr of age (Amaral and Dent 1981; Ribak et al. 1985; Seress and Mrzljak 1992; Seress and Ribak 1995). Functional connectivity can be inferred through the EEG, a dynamic measure of brain maturity (Marshall et al. 2002) with certain EEG patterns appearing as a function of age (Marshall et al. 2002). By age 2 yr, the EEG is quite similar to that of a young adult, with a well-developed, reactive θ rhythm of 7–8 Hz, distinct centro-parietal rhythms and well-formed frontally dominant fast activity. Sleep spindles, brief distinct bursts of 10–15 Hz activity with a characteristic waxing and waning shape, are a key element of the EEG used to identify the onset of sleep and represent a gating function that signals deepening disengagement from the surrounding environment. In addition, spindles are believed to play an important functional role in sleep-dependent synaptic plasticity and memory consolidation (Fogel and Smith 2011). The morphology and oscillatory frequency of spindles are used as markers of the developing brain (Shibagaki et al. 1982; Nicolas et al. 2001; Crowley et al. 2002; Martin et al. 2013). By age 2 yr sleep spindles are well developed and do not change in density with increasing age (McClain et al. 2016).

The EEG has excellent temporal, but poor spatial resolution due to volume conduction of electrical sources to the scalp (Nunez and Westdorp 1994; Babiloni et al. 1995). While investigators are beginning to examine the functional connectivity of neural networks underlying declarative memory using functional MRI and magnetoencephalography (MEG) (Taylor et al. 2012; Satterthwaite et al. 2014), these methods are difficult to implement in toddlers and young children. Therefore, understanding the molecular, cellular, and network underpinnings of spatial cognition requires the use of animal models, with the information extrapolated back to children. To this end, we describe below the development of spatial memory in rodents while providing the underlying neurobiological substrates and developmental trajectories of spatial memory systems.

Development of spatial memory in rats

Maneuvering safely through the environment is central to survival of almost all species. The ability to do this depends on learning and remembering locations. As with children, this capacity is encoded in the brain by two systems: one using distal cues outside the organism, allocentric navigation, and one using self-movement, internal cues, egocentric navigation (Vorhees and Williams 2014). This form of memory is tested in laboratory animals in many ways, including the T-maze, radial maze, Morris water maze, novel object location test, active avoidance test and Barnes maze.

Rats can use both "proximal" and "distal" cues to locate goal objects in their environments (Morris 1981; Rudy et al. 1987). In the proximal-cue situation, local stimuli that spatially cooccur with the goal are available to guide behavior. In the distal-cue situation, there are no cues that cooccur with the goal object; thus, to directly locate the goal, the rat must learn the spatial location of the goal relative to distal cues. These two navigation behaviors are dissociated during ontogeny. At postnatal (P) day 17 rats can use proximal cues to locate a safe platform. It is not until the rats are P20 that they demonstrate minimal evidence of distal-cue utilization (Rudy et al. 1987). These studies suggest that rat spatial navigation systems use egocentric navigation prior to P20 at which point allocentric spatial navigation skills emerge. Following the emergence of allocentric spatial skills there is a maturation of those skills until adult function is reached at approximately P40 (Schenk 1985; Brown and Kraemer 1997; Rossier and Schenk 2003).

Physiological underpinnings of spatial memory in rodents

While the electrophysiological basis of allocentric spatial memory is complex, involving many neuronal ensembles and pathways, key anatomical and physiological processes sub-serving spatial memory are briefly reviewed here.

The hippocampus and EC are the two structures that have the most critical role in spatial cognition. The EC functions as a hub in a widespread network for spatial memory and is the main interface between the hippocampus and neocortex. The medial EC (mEC) and hippocampus interactions play an important role in spatial memories including memory formation, memory consolidation, and memory optimization in sleep. The superficial layers—layers II and III—of mEC project to the dentate gyrus and hippocampus: Layer II projects primarily to dentate gyrus and hippocampal region CA3; layer III projects primarily to hippocampal region CA1 and the subiculum (Dolorfo and Amaral 1998a,b). These layers receive input from other cortical areas, especially associational, perirhinal and parahippocampal cortices, as well as prefrontal cortex. The lateral EC projects to the dentate gyrus, CA3 and CA1 and processes information about individual items based on a local frame of reference, primarily using external sensory information (Knierim et al. 2014). The lateral EC provides the hippocampus with information about the content of an experience. Thus, as a whole, the EC receives highly processed input from every sensory modality, as well as input relating to ongoing cognitive processes.

A key cell type recorded in layers II and III of the mEC are grid cells (Fyhn et al. 2007; Moser et al. 2015; Rowland et al. 2016). Grid cells are principal neurons that have multiple precisely tuned firing fields which collectively signal the rat's changing position with an accuracy similar to place cells in the hippocampus. When these cells are recorded in a large two-dimensional environment, each neuron forms a periodic triangular array, or a "grid," that covers the entirety of the environment (Hafting et al. 2005) An important property of the mEC representation is the stereotypic manner across environments, regardless of the environment's particular landmarks (Hafting et al. 2005; Fyhn et al. 2007). The strict structure of the map and its independence from external cues indicate that firing positions must be integrated in these cells from speed and direction signals, without reference to the external environment, a process referred to as "path integration" (McNaughton et al. 2006).

The majority of the principal cells in layers II and III of the mEC have grid properties (Sargolini et al. 2006). Thus, most of the spatially selective cortical input to the hippocampus originate from the mEC grid cells. Within the hippocampus many of the cells receiving input from the mEC grid cells are neurons that fire action potentials (APs) that correspond to the animal's location within its environment and are therefore called place cells (O'Keefe and Dostrovsky 1971; O'Keefe 1973; Muller 1996; Hok et al. 2007). Specifically, these hippocampal pyramidal neurons selectively discharge when the animal enters the cell's firing field. Unlike grid cells, a given place cell will have only one, or a few, place fields in a typical small laboratory environment, but more in a larger region (Fenton et al. 2008). Because of the robust relationship between the activity of these "place cells" and the ongoing spatial behavior of rats (Muller 1996; Eichenbaum et al. 1999; Lenck-Santini et al. 2001, 2002; Dragoi and Buzsáki 2006) such signals provide the animal with an internal spatial representation, or cognitive map (O'Keefe and Nadel 1978; Muller 1996; O'Keefe et al. 1998; Hok et al. 2007) that guides spatial navigation.

Place cells are characterized by their precise temporal firing relationship within local hippocampal θ oscillations (Skaggs et al. 1996; Lenck-Santini and Holmes 2008). The extracted phase of local θ can be combined with APs from a rate map (Fig. 1A, next page) to create a phase map (Fig. 1B). Phase maps demonstrate that APs of the cell tend to fire at the later phases of θ at the periphery of the field and then precesses to earlier phases of θ as the animal moves through the field. Taken together, the rate and phase map illustrate that APs in the center of the field, where most of the APs occur, fire in a phase range between 240° and 320°, agreeing with the rose plot (Fig. 1C), which shows that most APs fall within this phase range. Importantly, phase preference is dependent on the task. There is a shift in preferred phase of firing of a place cell in CA1 within the local θ cycle depending on the task the animal is doing. There are differences in phase preference when the animal is foraging for food pellets, a nonhippocampal task, and when the animal is engaged in a hippocampal-dependent task, such as the active avoidance test. In this test the animal uses spatial cues in the room to avoid a shock zone, which requires a heavy cognitive load (Fig. 1D). During a foraging session the cell's preferred position is in the ascending phase of θ while the same cell's preferred firing position during active avoidance, is in the descending phase of θ. As seen in Figure 1D, the rose plot histogram demonstrates a shift of phase preference from ~150° in foraging to ~240°–270°.

The phase of firing in CA1 has an important role in the encoding and recall of information (Hasselmo 2005; Hasselmo and Stern 2014; Siegle and Wilson 2014; Kleen et al. 2016). Input from the EC, the major source of cortical projections to the hippocampus, is highest at the peak of local θ (Brankačk et al. 1993; Kamondi et al. 1998; Hasselmo and Stern 2014) and likely encodes sensory information from the environment (Hasselmo 2005; Hasselmo and Stern 2014). At this same phase, the hippocampus is more susceptible to long-term potentiation (LTP) (Hyman et al. 2003; Kwag and Paulsen 2009), which is consistent with the idea that this phase is optimized for encoding new information. At the trough of local θ, CA1 cells receive greater input from CA3 (Hasselmo 2005; Hasselmo and Stern 2014). At this phase, stimulation of Schaffer collateral or temporoammonic inputs induces long-term depression (LTD) (Hyman et al. 2003; Kwag and Paulsen 2009), which could suppress information storage during memory retrieval.

Theta (6–12 Hz in rats) rhythm and γ oscillations (25–100 Hz) rhythms are critical oscillations in the neurophysiology of spatial cognition. Theta (6–12 Hz in rats) is essential for the formation

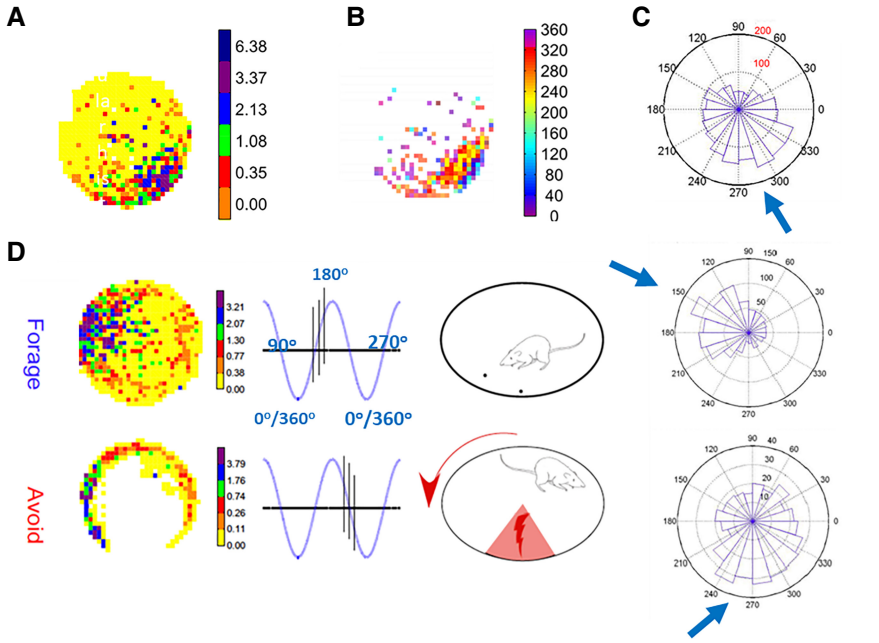

Figure 1. Place cell AP phase preference with regard to local θ. (*A*) AP firing rate map with median firing rate per pixel for a single place cell. (*B*) Phase map indicating the median phase of θ for APs in each pixel. (*C*) Rose plot circular histogram indicating the place cell's preferred firing phase with θ. The phase map in *B* indicates that the APs tend to fire earlier in the θ cycle as the animal moves through the firing field. The higher firing rates correspond to phases between 240°–320° (arrow), consistent with the rose plot in *C*. (*D*) Shift in preferred phase of firing of a hippocampal place cell within the θ cycle between foraging and avoidance contexts. During foraging the cell fired in the ascending phase of θ. During active avoidance session the cell shifted firing to the descending phase of θ. Rose plot histogram demonstrates a shift of phase preference from ~150° in foraging to ~240°–270° in active avoidance (arrows).

and segregation of neuronal assemblies necessary for spatial memory (Winson 1978; Buzsáki 2002; Gupta et al. 2012) and is present in rat pups during the first week of life (Karlsson and Blumberg 2003). Spatial cognition processing is also dependent on γ oscillations, rhythmic fluctuations in local field potentials (LFPs) that span a broad range of frequencies (25–100 Hz) (Colgin and Moser 2010) and are present in the first week of life (Quilichini et al. 2012). Two functionally distinct rhythms, slow (25–50 Hz) and fast (55–100 Hz) γ (Colgin et al. 2009; Colgin 2016) are present in the hippocampus. These different frequencies of γ rhythms are thought to be locally generated by GABAergic interneurons (Colgin 2016; Mably and Colgin 2018). While slow and fast γ are locally generated, γ oscillators exhibiting similar frequencies in different brain regions can become coupled by anatomical connections between structures (Mably and Colgin 2018). Fast γ rhythms in the hippocampus are coupled with fast γ inputs from the mEC (Colgin et al. 2009). Fast γ (50–140 Hz) reflects entorhinal cortex-CA1 circuit innervation and contributes to memory encoding (Colgin et al. 2009; Colgin 2015, 2016) while slow γ (25–50 Hz) reflects CA3–CA1 circuit innervation and contributes to memory retrieval (Colgin et al. 2009; Colgin 2016).

In addition to θ and γ oscillations, a major network oscillation pattern in the hippocampus are "sharp waves and ripples" (SWRs). SWRs are large amplitude (0.5–1.5 mV) negative polarity field potentials with a duration of 40–100 msec occurring in the CA1 stratums radiatum (Buzsáki 1986). SWRs emerge at the end of the second postnatal week in rats (Buhl and Buzsáki 2005). The sharp waves are usually associated with a short-lived fast oscillatory pattern fast-field oscillations (~140 to 200 Hz), so-called "ripples" confined to the CA1 cell layer (O'Keefe and Nadel 1978; Buzsáki et al. 1992; Traub et al. 2000). SWRs are endogenous events that occur when the animal has no or minimal interaction with the environment, such as during slow wave sleep, immobility and consummatory behaviors (Buzsáki et al. 1983). During sleep, hippocampal network activity recapitulates patterns observed during recent experience: place cells with overlapping spatial fields show a greater tendency to cofire ("reactivation") (Wilson and McNaughton 1994). The temporally ordered and compressed sequences of place cell firing observed during wakefulness are reinstated ("replay") during SWRs (Skaggs and McNaughton 1996; Nádasdy et al. 1999; Lee and Wilson 2002). It has been suggested that this reactivation or replay of sequential APs may underlie memory consolidation (Girardeau et al. 2009; Dupret et al. 2010; Ego-Stengel and Wilson 2010; McNamara et al. 2014).

Construction of networks supporting spatial memory in rodents

The ontogeny of spatial memory in rodents is highly orchestrated with critical periods where axons and dendrites need to establish appropriate connections that optimizes information processing across broad networks (Sporns et al. 2004; Sheperd and Grillner 2018). This task is largely accomplished during embryonic and early postnatal development, when specific network architectures supporting the production of appropriate receptive fields are generated. Two main mechanisms participate in assembling neuronal networks. First, the expression of specific ligands and receptors guides axons and dendrites to their innervation territories, and promote the formation of synapses (Stoeckli 2018). Second, stereotyped patterns of activity propagate through developing circuits to refine cell-to-cell functional connectivity (Stryker and Harris 1986; Kirkby et al. 2013). The combination of these two processes—finding the proper partners and giving rise to networks that can efficiently process information—make spatial cognition possible.

The mechanisms underlying the assembly of neural circuits have been extensively studied for sensory systems, especially those devoted to vision. Here, axons from ganglion cells take an intricate route to leave the retina and reach specific territories of the thalamus and the superior colliculus (Godement et al. 1984). In turn, thalamic axons follow their own intricate path to reach a specific portion of the cortical anlage, what will become the primary visual cortex (Parnavelas and Chatzissavidou 1981). A series of attractant or repulsive signals guide these axons toward their specific targets; Robo/Slit, NrCam, Netrins, Ephs and ephrins, and many other molecules have been implicated in this process (Brittis et al. 1995; Brown et al. 2000; Erskine et al. 2000; Afari et al. 2014; Erskine and Herrera 2014). This elegant process is not sufficient on its own to produce the sophisticated network architecture that supports vision. To create an internal representation of the sensory space, the visual system is designed to allow for an accurate representation of the visual scene. Specifically, two visual inputs that are nearby in space and stimulate proximate portions of the retina, are represented by neighboring cells in multiple areas of the visual system giving rise to a coherent topographical map of

the stimulus (Schuett et al. 2002). Connections between neighboring cells must therefore be strengthened, while connections between cells that are located further away from each other must be weakened. To achieve this aim, intrinsically generated patterns of activity cross the sensory areas like "waves" to optimize the synaptic matrix of the network for the representation of visual stimuli (Meister et al. 1991; Wong et al. 1995; Katz and Shatz 1996; Ackman et al. 2012; Kirkby et al. 2013). The fact that sensory organs dominate the initiation of these waves, which propagate through the nervous system to reach the neocortex (Ackman et al. 2012), suggest that the sensory receptor-bearing cells drive the maturation of extended neural networks devoted to sensory perception.

As neural ensembles move further and further away from the sensory organ, topographic organization is not evident and receptive fields arise because of locally produced computations. The mEC-hippocampal system is one such network. Located at a great synaptic distance from sensory epithelia, this network sits on top of the cortical hierarchy and integrates multisensory stimuli to produce cell types whose firing is coded to specific locations of the environment or aspects of navigation. The mEC creates a neural representation of space through a set of functionally dedicated cell types: grid cells, border cells, head direction cells, and speed cells (Felleman and Van Essen 1991; van Strien et al. 2009; Rowland et al. 2016) with the rate of maturation unique to each type of neuron (Tan et al. 2017). Grid cells first emerge around P21 and develop functional properties rapidly. As soon as grid cells can be detected, they possess almost all of the properties that characterize adult grid cell firing (Wills et al. 2012). Individual grid cells may mature over the course of approximately 1 d. At P22–23, the percentage of mEC cells classified as grid cells reaches a similar level to adults (Wills et al. 2010). Furthermore, in vitro recordings show that mEC stellate cell network synchronization significantly increases at P22 (Langston et al. 2010). This suggests that the widespread recurrent excitatory network thought to be necessary for grid cell activity emerges at this age (Fuhs and Touretzky 2006; McNaughton et al. 2006; Burak and Fiete 2009).

While the first adult-like grid cells are present at weaning, place cells show spatially tuned and stable firing at least 4 d earlier at ~P16 (Langston et al. 2010; Wills et al. 2010). Before weaning, offline place cell activity replay with SWRs reflects predominantly stationary locations in recently visited environments. The place cell representation of space is denser, more stable, and more accurately close to environmental boundaries. A putative stabilizing signal to place cells before grid cells emerge are boundary-responsive cells. mEC boundary cells emerge at P17 and drive stable place cell firing before weaning (Wills et al. 2010; Bjerknes et al. 2014). In contrast, sequential place cell firing, describing extended trajectories through space during exploration (θ sequences) and subsequent rest (replay), emerge gradually after weaning in a coordinated fashion (Muessig et al. 2019). This developmental switch in place cell accuracy coincides with the emergence of the grid cell network in the mEC, suggesting that grid cells contribute to stable place fields when an animal is far from environmental boundaries (Muessig et al. 2015). This developmental switch in place accuracy also coincides with the development of allocentric spatial memory in rodents. Figures 2 and 3 provide schematics showing timing of development of key factors involved in spatial memory and the relationship between EC and hippocampal cells and oscillatory activity.

The mechanisms that produce spatially tuned firing patterns are still unknown, but likely rely on the interplay between the hippocampus and the mEC. Silencing one part of the network severely affects spatial representations produced by the other (Bonnevie et al. 2013). Based on these premises, it is proposed that the spatially tuned firing of grid and place cells arises from local computations as a result of the specific synaptic architecture of the network (Martin and Berthoz 2002; McNaughton et al. 2006; Couey et al. 2013; Moser et al. 2014). Furthermore, it has been hypothesized that patterned activity propagating through the mEC-hippocampal circuit during a sensitive developmental phase finely tunes synaptic connectivity of the network, and drives the emergence of specific firing patterns (McNaughton et al. 2006; Kropff and Treves 2008). As described above, the firing patterns of grid and place cells evolve and mature during postnatal development (Langston et al. 2010; Wills et al. 2010; Scott et al. 2011; Muessig et al. 2015).

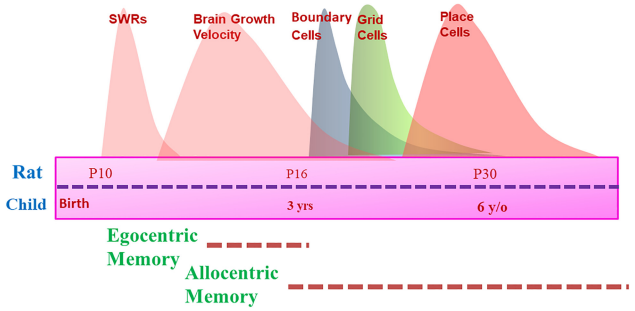

Figure 2. Schematic showing timing of development of key factors involved in spatial memory. As boundary, grid and place cells develop there is a transition from egocentric to allocentric memory.

Multiple molecular signals are involved in setting up connectivity across the areas that belong to the mEC-hippocampal network. Cells located in the mEC establish their projections to the hippocampus during embryonic life. mEC axons can be backlabelled from the hippocampus by embryonic (E) day15 and innervate the dentate gyrus by E18 (Supèr and Soriano 1994). To reach their destination, mEC fibers use a scaffold that is created by Cajal-Retzius cells located in the hippocampus. These cells create a "trail" on which EC axons can grow and provide the substrate on which mEC axons can make synaptic contacts (Ceranik et al. 1999). The commissural axons originating from the hippocampal subfields are formed later, between E18 and P2 (Supèr and Soriano 1994) and use a plethora of molecular signals (including Semaphorins, Neuropilin, Slits, and Ephrins [see Skutella and Nitsch 2001]) to find their targets. However, due to a protracted period of neurogenesis and synaptogenesis that extends into postnatal life, reaching an adult-like level at the end of childhood (Deguchi et al. 2011; Donato et al. 2017), the connectivity matrix of the mEC-hippocampal network reorganizes extensively during the first postnatal month. During the same period, excitability influences synaptogenesis in each hippocampal subfields (Johnson-Venkatesh et al. 2015), with patterned activity being generated at multiple stages of the network (Garaschuk et al. 2000; Leinekugel et al. 2002; Crépel et al. 2007).

Correlated activity in the mEC-hippocampal neuronal networks, supported by oscillatory and intermittent population activity patterns is critical for learning and memory. However, when and how correlated activity emerges in these networks during development remains largely unknown. During the first postnatal week in nonanaesthetized head-restrained rats, activity in the superficial layers of the mEC and hippocampus is highly correlated, with intermittent population bursts in the mEC followed by early SWRs in the hippocampus (Valeeva et al. 2018). Neurons in the superficial mEC layers fired before neurons in the dentate gyrus, CA3 and CA1. Current-source density profiles of early SWRs indicate that performant path and temporoammonic entorhinal inputs and intrinsic hippocampal connections are coactivated during mEC-hippocampal activity bursts. Most mEC-hippocampal

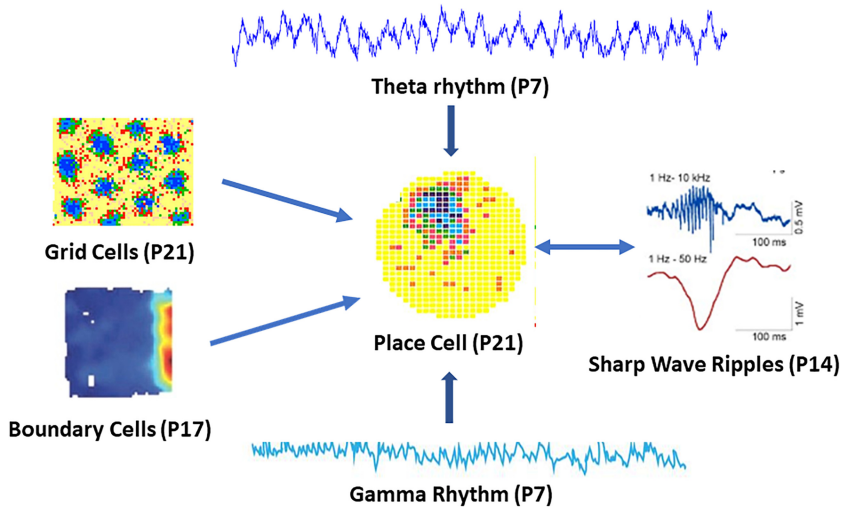

Figure 3. Schematic showing relationship between place cells and EC cells and oscillations. mEC boundary cells emerge at P17 and drive stable place cell firing before weaning. Grid cells emerge by P21 and stabilize place cells away from boundaries resulting in allocentric navigation. θ and γ activity, which are present in the first postnatal week, add the dimension of temporal coding to place cell firing. During sharp wave ripples which are present by the second postnatal week result in replay of APs during sleep or awake states.

bursts are triggered by spontaneous myoclonic body movements. Thus, during the neonatal period, activity in the mEC and hippocampus is highly synchronous, with the mEC leading to hippocampal activation. It is proposed that such correlated activity is embedded into a large-scale bottom-up circuit that processes somatosensory feedback resulting from neonatal movements, and that it is likely to instruct the development of connections between neocortex and hippocampus. Indeed, a similar process has been proposed for the development of the somatosensory circuit (Khazipov et al. 2004). In rat pups, spatially confined spindle bursts are selectively triggered in a somatotopic manner by spontaneous muscle twitches, motor patterns analogous to human fetal movements (Khazipov et al. 2004).

Important questions arising from these findings pertain to how excitatory activity influence the maturation of the mEC-hippocampal system. Maturation of the mEC-hippocampal network follows a stereotyped sequence, where layer 2 of the mEC is the first area to mature, followed by CA3, CA1, dentate gyrus, subiculum, layer 5 of the mEC and layer 2 of the lateral EC (Fig. 4; Donato et al. 2017). At each stage of the circuit, excitatory activity drives the maturation of downstream areas of the network in a linear and directional developmental sequence. This sequence originates in mEC layer 2, where maturation of stellate cells precedes that of other excitatory cell types in the circuit. Silencing stellate cells arrests the maturation of excitatory and inhibitory neurons at every stage of the mEC-hippocampal network; in stark contrast, silencing pyramidal cells did not. This leads to the conclusion that stellate cells in mEC drives the maturation of the mEC-hippocampal network. The stellate cells are the source of an activity-dependent signal that propagates stage-wise through the network to promote structural maturation of excitatory and inhibitory neurons. Whereas the excitatory actions in the mEC-hippocampus drives synaptic development and connectivity, it is important to note that excessive excitability can be detrimental to developing neural circuits, as will be described below.

Disruptions of developing networks supporting spatial memory in rodents

As noted above, there is a precise timing of developmental events that depend on genetic and activity-dependent mechanism to assure normal connectivity of the brain leading to normal spatial cognition. Recent evidence has indicated there is a critical period for processing memories which depends on activity and plasticity mechanisms within the developing hippocampus (Travaglia et al. 2016a,b). For example, the activity-regulated and memory-linked gene Arc/Arg3.1 is transiently up-regulated in the hippocampus during the first postnatal month. Conditional removal of Arc/Arg3.1 during this period permanently alters hippocampal oscillations and diminishes spatial learning capacity throughout adulthood (Gao et al. 2018). In contrast, post developmental removal of Arc/Arg3.1 leaves learning and network activity patterns intact. Long-term memory storage continues to rely on Arc/Arg3.1 expression throughout life. These results indicate there are critical period for spatial learning, during which Arc/Arg3.1 foster maturation of hippocampal network activity necessary for future learning and

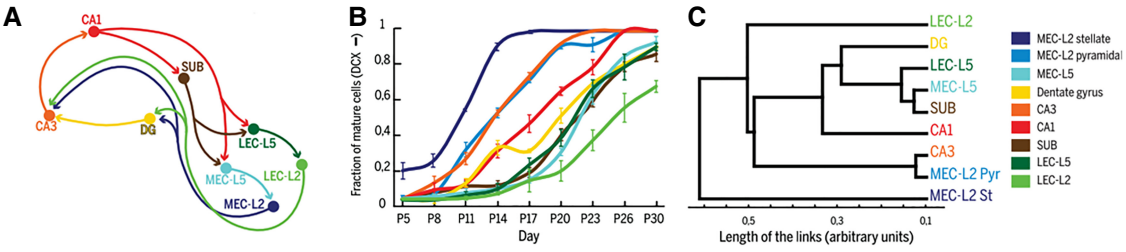

Figure 4. Stagewise sequential maturation of the entorhinal-hippocampal network (Donato et al. 2017). (*A*) Schematic representation of information flow in the transverse entorhinal-hippocampal circuit. (*B*) Fraction of neurons with doublecortin (DCX) expression levels below the detection limit in each local network during successive days of maturation (DCX cumulative distributions, means ± SD). DCX is a microtubule-associated protein that is present in neuronal precursors and immature neurons, where it promotes dendritic growth and is down-regulated during the stabilization of synaptic connectivity at late developmental stages. (*C*) Hierarchical clustering of data in (*B*); *x*-axis length of the links of the dendrogram, arbitrary units. mEC layer (L) 2 striatal cells (MEC-L2 St) are the first population to exhibit dissimilarity from the rest of the network, followed by (i) MEC-L2 pyramidal (Pyr) and CA3, (ii) CA1, (iii) dentate gyrus, subiculum (SUB), MEC-L5, and LEC-L5, and (iv) LEC-L2.

memory storage. These critical principles of memory network development and maturation are fundamental to our understanding of how aberrant activity patterns early in life may lead to disrupted structural and functional maturation of the same circuits.

There are multiple pathological conditions that can disrupt the normal development of spatial memory. Genetic causes such as Fragile X, Rett syndrome and Angelman syndrome can result in maldevelopment of networks serving spatial cognition (Dan et al. 2015). The Ube3a mouse model of Angelman syndrome, the Ts65Dn trisomy mouse model of Down syndrome, the FXS model of Fragile X syndrome and the Mecp2Bird mouse model of Rett syndrome have demonstrated deficits in spatial cognition (Gomi et al. 2010; Sun et al. 2016; Leach and Crawley 2018). Acquired insults such as hypoxia, trauma or infections can also produce pronounced deficits in spatial cognition. The mechanisms of these disruptions vary depending on the genetic or acquired insult involved. Here, we focus on the role of aberrant activity during critical developmental period in provoking enduring memory problems. We focus on a clinically relevant type of aberrant network activity: the synchronized bursts of massive numbers of neurons that fire together during seizures.

Whereas normal activity patterns are required for circuit maturation, aberrant neuronal activity is known to disrupt spatial cognition (Davis et al. 2017). This is particularly important in the case of massive bursts of synchronized network activity which occur during seizures. The effects of seizures on the development and integrity of memory circuits is of major clinical relevance; one of the more common neurological conditions in children is epilepsy. Although seizures are the most striking clinical manifestation of the epilepsies, children with epilepsy are at risk not only for seizures but also for a myriad of comorbid health problems that occur at a higher rate than would be expected by chance. Among the comorbidities associated with childhood epilepsy, memory disturbances are among the most common and troublesome (Hermann et al. 2002; Holmes 2015).

Seizures associated with fever in children, when longer than 30 min (termed febrile status epilepticus or FSE), can lead to epilepsy that involves the hippocampal circuit (temporal lobe epilepsy). Importantly, recent work in children (Weiss et al. 2017) has identified memory problems in children who sustained FSE even before the onset of epilepsy, suggesting that memory functions and the underlying circuits were directly impacted by the FSE.

To probe the causal relationship of FSE and memory problems, and uncover the mechanisms, an experimental FSE (eFSE) model has been created and heavily adopted and validated (Dubé et al. 2000, 2012; Dubé and Baram 2006; McClelland et al. 2011). eFSE is generated by elevating brain temperature to 38°C–29°C, temperatures generating seizures in children. The hyperthermia is needed because induction of fever is not possible in infant rats (Dubé et al. 2007), though some elevation of brain temperature using lipopolysaccharide administration has been described (Heida et al. 2009). Notably, inflammatory cytokines are induced and are involved in these febrile-like seizures (Dubé et al. 2005; Vezzani et al. 2011a). To mimic childhood FSE, hyperthermia is maintained for ~60 min, resulting in seizures lasting 40–50 min. eFSE is generated via hyperthermia, because induction of fever is not possible in infant rats (Dubé et al. 2007). However, inflammatory cytokines are induced and are involved in these febrile-like seizures (Dubé et al. 2005; Vezzani et al. 2011a,b). To mimic childhood FSE, hyperthermia is maintained for ~60 min, resulting in seizures lasting 40–50 min. These seizures provoke memory deficits during adolescence and in adulthood, including, notably, impaired spatial cognition (Dubé et al. 2006, 2009; Barry et al. 2016a,b; Patterson et al. 2017). Importantly, no cell loss occurs following eFSE, yet neuronal structure in hippocampus is affected, including dendrite loss in CA1 and aberrant generation of excitatory synapses in dentate gyrus granule cells (Patterson et al. 2017). The presence of spatial memory and structural deficits after eFSE provides a unique opportunity to study how aberrant patterns of network activity during development disrupt the maturation of memory networks.

Spatial cognition following eFSE is tested in the active avoidance task, a systems-level task where animals learn to associate an unmarked region of space with a mild shock on a constantly rotating arena (Baglietto et al. 2001; Pastalkova et al. 2006; Popp et al. 2011; Barry et al. 2015, 2016a). Control rats rapidly learn the spatial location of the shock-zone using spatial cues which surround the rotating arena, whereas eFSE rats received significantly more shocks than controls, suggesting that they are not able to effectively learn and remember the location of the shock quadrant. A second measure of spatial learning in this task is the time spent in the quadrant opposite the shock zone, indicating a spatial strategy used to avoid shocks. eFSE rats spend significantly less time in the opposite quadrant as compared to controls, suggesting that these animals used a less efficient, potentially nonspatial strategy to avoid shocks (Barry et al. 2016a).

These memory problems are associated with clear electrophysiological aberrations of the network (Patterson et al. 2017). Following eFSE, speed/θ correlations (θ frequency normally increases with speed of running) are reduced dramatically. Both fast and slow γ frequency and amplitude were abnormal in eFSE rats and correlated with learning and memory deficits. In aggregate, the findings indicate that the balance of routed neural information to CA1 from the EC (fast γ) and CA3 (slow γ) is disrupted by eFSE, interfering with both the acquisition of spatial information believed to be associated with mEC inputs and the recall of information believed to be associated with CA3–CA1 input.

Following eFSE there are also abnormalities in temporal coding (Barry et al. 2016a). As shown in Figure 5, during foraging, which does not require hippocampal involvement, CA1 place cells from controls fire near the peak of local θ, whereas during active avoidance, which is a hippocampal-dependent task, the CA1 cells fire at later phase of θ that is more in register with a static θ phase preference in CA3 (Barry et al. 2016a). The population of CA1 place cells from eFSE rats do not exhibit a preferred phase of firing during either foraging and active avoidance. Phase coupling, that is the coordinated firing of APs in CA3 and CA1 at the same phase of θ, is thus greater in the controls than in the eFSE rats. Both the absence of phase preference in CA1 and inability to shift phase preference to align APs in both CA3 and CA1 circuits during a hippocampal-dependent task, indicate neuronal discoordination provoked by the eFSE. Insufficient coordination between structures in the hippocampal circuit by θ oscillations prevent the eFSE rats from accurately calculating their position during the active avoidance task.

The molecular mechanisms by which early-life seizures lead to disruptions at the cellular and network levels are emerging. Recently, it was discovered that eFSE provokes coordinated, transcriptionally regulated changes in the expression of a relatively small set of genes governing neuronal behavior. These changes result from augmented function of the neuron-restrictive silencing factor (NRSF), which is uniquely situated among numerous brain transcription factors to mediate neuronal plasticity after eFSE (McClelland et al. 2011, 2014; Patterson et al. 2017) due to its unique role in neuronal maturation and in the function of mature neurons. NRSF expression was originally described in nonneuronal tissues where it suppresses neuron-specific genes (Schoenherr and Anderson 1995; Chen et al. 1998). This role predicted that many neuronal genes must carry NRSF-response elements (NRSEs) and will therefore be repressed by augmented NRSF (McClelland et al. 2014). Recently, low levels of NRSF however expression in mature neurons has been described, where the factor may be crucial for normal function (Ballas et al. 2005; Ballas and Mandel 2005; Gao

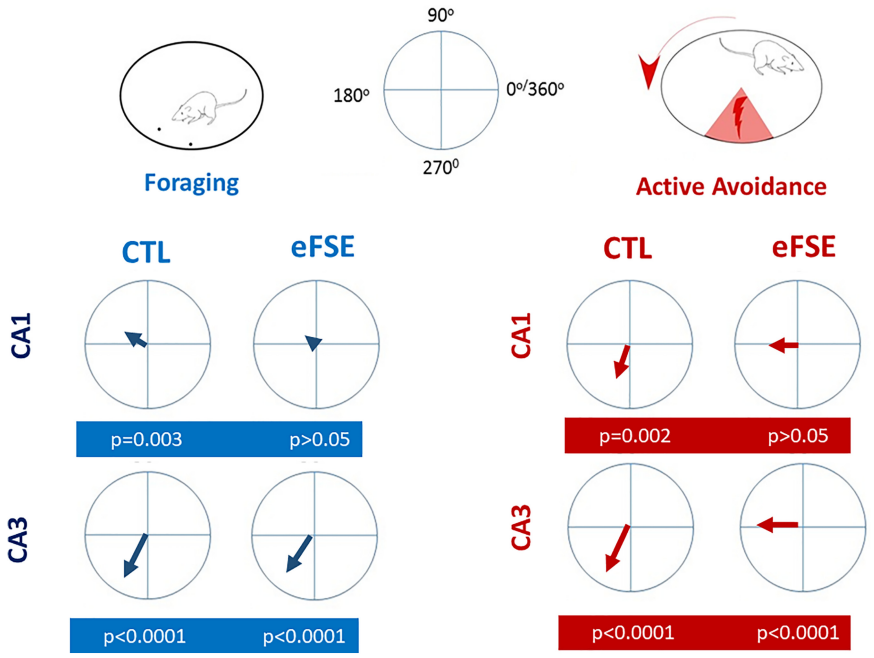

Figure 5. Distribution of preferred firing phases for place cells recorded during foraging sessions in CA1 (*Top*) and CA3 (*Bottom*) from control (CTL) and eFSE animals. CTL CA1 cells showed a significant phase preference at 214° while eFSE cells had a mean, nonsignificant, phase angle preference of 194°. CTL CA3 cells had a significant phase preference toward the descending phase of θ (257°) as did eFSE animals (226°). During active avoidance CTL CA1 cells significantly shifted phase preference to the descending phase of Θ at 260° while eFSE CA1 cells exhibited a lack of phase preference. CTL CA1 phase preference shifts away from peak Θ puts cell firing preference in CA1 and CA3 in alignment.

et al. 2011). Tight regulation of NRSF levels is especially crucial to developing neurons, where expression of NRSF-regulated genes contributes to several aspects of maturation, including development of excitatory synapses (Schoenherr and Anderson 1995; Chen et al. 1998; Yang et al. 2012). This is important because FSE takes place during the developmental epoch (infancy and early childhood in humans, P10–11 in the rat (Avishai-Eliner et al. 2002), when many brain neurons are largely mature but when specific neuronal populations, including granule cells in the dentate gyrus, are still differentiating and maturing (Schlessinger et al. 1975; Thind et al. 2008).

NRSF activity is dramatically augmented after eFSE, leading to repression of a number of important genes, such as those coding for ion channels, glutamate receptors, synaptic proteins, and others (McClelland et al. 2014; Brennan et al. 2016). To test directly if NRSF-overactivity contributed to the disruption of memory circuits provoked by eFSE NRSF function was blocked through use of deoxyoligonucleotides (ODNs) which binds to NRSF and prevents it from reaching and binding the DNA of target genes (Patterson et al. 2017). Hippocampal

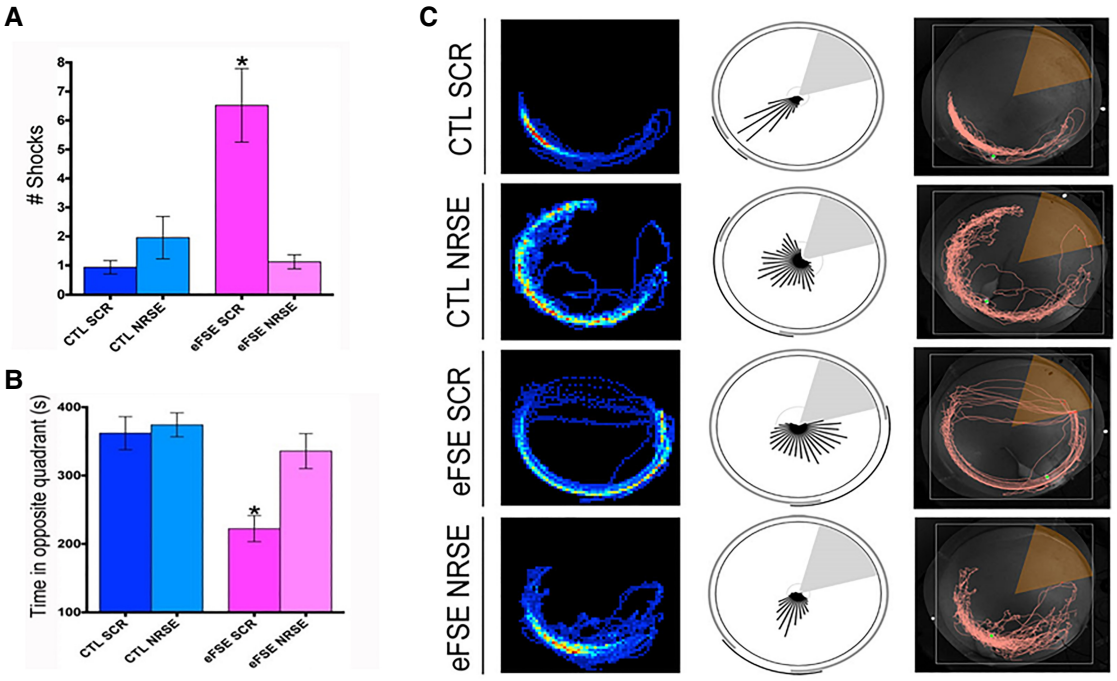

Figure 6. eFSE provokes persistent impairment of spatial memory in active avoidance which is abrogated by blocking NRSF after eFSE (Patterson et al. 2017). (*A*) eFSE rats treated with a SCR ODN received more shocks than both control groups (CTL + SCR ODN, CTL + NRSE ODN), as well as from eFSE rats treated post hoc with a blocker of NRSF (eFSE + NRSE ODN). (*B*) Similar results are obtained when assessing the duration of time spent in the opposite quadrant to the shock zone. The eFSE + SCR group spent less time in the opposite quadrant than the other three groups. (*C*) Representative traces of movement of rats from each of the four groups.

network oscillatory activity and temporal coding during active avoidance testing was then assessed in young adult rats that had experienced eFSE. Notably, the administration of specific NRSE ODN prevented the spatial deficits seen in eFSE rats. The memory performance of rats receiving NRSE ODN was indistinguishable from the controls in the active avoidance task (Fig. 6). Rats receiving scrambled ODN, which consist of ODNs that do not block NRSE and thus serve as a control injection, had spatial deficits following the eFSE.

NRSF blockade following eFSE also enhanced slow γ oscillations and prevented abnormalities in speed/θ correlation coefficients (Patterson et al. 2017), in parallel to restoring memory function. Blocking NRSF also rescued the structural maturation of dentate gyrus granule cells. Thus, blocking NRSF transiently after eFSE prevented granule cell dysmaturation, restores a functional balance of γ-band network oscillations, and allows treated eFSE rats to encode and retrieve spatial memories. Together, this work provides novel insights into both the normal construction of networks that underlie memory as well as the mechanisms by which early-life seizures in rodents disrupt this maturation. While it is unlikely that ODNs will be used to treat children with FSE, understanding the molecular signaling that results in spatial cognitive deficits provides a roadmap to exciting future therapeutics.

Conclusions

In children, allocentric spatial memory emerges around 22 mo of age whereas in rats allocentric spatial memory develops between P20–P25. Allocentric spatial memory in rats coincide with the functional maturation of place cells. The developmental switch in place cell accuracy coincides with the emergence of the grid cell network in the EC, and mechanistic studies indicate that grid cells contribute to stable place fields. The ontogeny of spatial memory in rodents is highly orchestrated and includes sensitive periods during which axons and dendrites need to establish appropriate connections that optimize information processing. The molecular signals responsible for these developing networks are increasing being identified. Whereas normal activity patterns are required for circuit maturation, there is now evidence that abnormal neuronal activity—including seizures—can disrupt this process resulting in aberrant connectivity and impaired signaling, manifesting as deficits in spatial cognition. Understanding the molecular and cellular bases for this disrupted maturation holds promise for preventative and therapeutic interventions.

Acknowledgments

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