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Development of the hippocampal CA2 region and the emergence of social recognition

Emma J. Diethorn | **Elizabeth Gould**

Princeton Neuroscience Institute, Princeton University, Princeton, New Jersey, USA

Correspondence
Elizabeth Gould, Princeton Neuroscience Institute, Princeton University, Washington Rd, Princeton, NJ 08544, USA.
Email: goulde@princeton.edu

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Abstract

Social memories formed in early life, like those for family and unrelated peers, are known to contribute to healthy social interactions throughout life, although how the developing brain supports social memory remains relatively unexplored. The CA2 subregion of the hippocampus is involved in social memory function, but most literature on this subject is restricted to studies of adult rodents. Here, we review the current literature on the embryonic and postnatal development of hippocampal subregion CA2 in mammals, with a focus on the emergence of its unusual molecular and cellular characteristics, including its notably high expression of plasticity-suppressing molecules. We also consider the connectivity of the CA2 with other brain areas, including intrahippocampal regions, such as the dentate gyrus, CA3, and CA1 regions, and extrahippocampal regions, such as the hypothalamus, ventral tegmental area, basal forebrain, raphe nuclei, and the entorhinal cortex. We review developmental milestones of CA2 molecular, cellular, and circuit-level features that may contribute to emerging social recognition abilities for kin and unrelated conspecifics in early life. Lastly, we consider genetic mouse models related to neurodevelopmental disorders in humans in order to survey evidence about whether atypical formation of the CA2 may contribute to social memory dysfunction.

KEYWORDS
CA2 region, development, hippocampus, social memory

1 | INTRODUCTION

In humans, social memories are crucial for dynamic social interactions, including those that occur in families, work settings, and community living. Social memory capabilities emerge during early life, typically beginning with an infant's ability to recognize its caregiver, and become more complex as development progresses. Across mammalian species, the ability to form and retain memories for members of the same species is crucial to survival, both during infancy and into adulthood. Social memory has been shown to involve the hippocampus in both primates and rodents (Montagrin et al., 2018; Okuyama, 2018). Studies in rodents have pinpointed the CA2 region of the hippocampus as critical for social recognition function (Hitti & Siegelbaum, 2014; Stevenson & Caldwell, 2014). No studies have causally linked the CA2 to social memory in other mammals, including humans, but indirect evidence supports the view that the function of this region is conserved across mammals (Han et al., 2019; Haukvik et al., 2018; Montagrin et al., 2018; Villard et al., 2021).

The anatomical organization of the CA2 region of mice, monkeys, and humans was first described almost a century ago by Lorente de Nó (1934), but its contribution to behavior has remained relatively understudied until recently. The lack of attention by the scientific community to this region was due mostly to the misconception that the CA2 is merely an intermediate zone between the CA1 and CA3. About 15 years ago, pioneering studies by the Dudek lab showed that the CA2 is functionally different from the CA1. These studies showed that, when compared to CA1, CA2 pyramidal cells are resistant to the induction of long-term potentiation (LTP) resulting from Schaffer collateral innervation onto dendrites in the stratum radiatum (Simons et al., 2009; Zhao et al., 2007). This work was followed by several studies showing that the CA2 possesses molecular and connectivity properties that do not exist in the neighboring CA fields, supporting the claim that it is a distinct subregion instead of a transition area (Carstens et al., 2016; Cui et al., 2013). Around the same time as a growing number of findings about gene expression patterns and connectivity of the CA2 were emerging, reports of specific behavioral and electrophysiological functions of the mouse CA2 came to light. These behavioral studies showed that silencing of CA2 in adulthood impaired the ability to recognize a recently encountered mouse as familiar (Hitti & Siegelbaum, 2014; Meira et al., 2018). Conversely, studies showed that activating the CA2 improved social recognition memory (Smith et al., 2016). Since rodents demonstrate an innate preference for novel social and nonsocial stimuli (Albasser et al., 2010; Moy et al., 2004), recognition of, and memory for, previously encountered stimuli are inferred by diminished investigation of the stimulus as it transitions from novel to familiar.

Electrophysiological studies have shown that, although the CA2 does not exhibit LTP under conditions that are known to induce it in the CA1 (Carstens et al., 2016; Simons et al., 2009; Zhao et al., 2007), it does show evidence of inhibitory long-term depression (iLTD) and input timing-dependent plasticity (ITDP) (Domínguez et al., 2019; Leroy et al., 2017; Piskorowski et al., 2016). The CA2 is also an important generator of sharp wave ripples (SWRs) (Oliva et al., 2016), high-frequency oscillatory events that have been linked to novelty recognition, as well as to memory consolidation and retrieval (Joo & Frank, 2018). Some evidence suggests that CA2 SWRs may be unusual relative to SWRs generated elsewhere in the hippocampus because they occur more frequently in the awake state (Oliva et al., 2016; Middleton & McHugh, 2016). CA2 SWRs have been causally linked to social recognition (Oliva et al., 2020), as have gamma oscillations (Alexander et al., 2018), suggesting that neuronal oscillations in this region underlie important aspects of sociocognitive processing.

Since initial reports of the role of CA2 in social memory, detailed studies have characterized the adult CA2, including its cellular and molecular composition (Carstens et al., 2016; Gerber et al., 2019; Hitti & Siegelbaum, 2014; Kohara et al., 2014). Despite this, a marked gap exists in our knowledge of how the CA2 develops in early postnatal life and what properties it possesses when social capabilities begin to emerge. In fact, until recently, very little was known about the development of social memory in rodents. It is evident that social recognition is critical to healthy social interactions across a mammal's life span. Children with autism spectrum disorders, and related conditions like Phelan–McDermid syndrome and Fragile X syndrome, demonstrate an impaired ability to recognize familiar individuals, which likely contributes to impaired social interactions throughout life (Guillory et al., 2021; Holsen et al., 2008; Williams et al., 2013). Similarly, adolescents with 22q11 deletion syndrome, a major risk factor of schizophrenia, consistently show impaired social memory and cognition in a range of tasks (Campbell et al., 2015), and mouse models recapitulating this condition exhibit a number of abnormalities in CA2 (Piskorowski et al., 2016). Thus, a review of the development of hippocampal CA2 structure and function may help to identify potential points of intervention during early life aimed at ameliorating dysfunction in individuals with impaired social recognition.

2 | SOCIAL RECOGNITION DURING DEVELOPMENT AND THE ROLE OF THE CA2 REGION

2.1 | Kin memory and social preference in mammals

Humans and other primates first form social memories for kin, including caregivers and siblings, using visual, auditory, and olfactory cues. Beginning soon after birth, these cues contribute to a newborn's ability to recognize its mother, identifying her from the sight of her face, the sound of her voice, and her unique olfactory mosaic (Burnham, 1993; Pascalis et al., 1995; Schaal et al., 2020). Throughout the first postnatal year, human infants prefer images of novel infant faces over familiar infant faces, but when shown images of siblings, they prefer them over novel infant faces. Human infants also prefer their mothers' faces over those of unfamiliar mothers (Bushneil et al., 1989; Damon et al., 2021). Together, these findings indicate that humans use a complex combination of identifying factors to recognize individuals, and this recognition manifests as a preference for familiar kin and, perhaps, for novel peers in early life.

Most rodents are altricial, born with eyes and ears fused shut, so the majority of their neonatal sensory input comes from smell, taste, and touch (Williams & Scott, 1954). Available evidence suggests that olfaction is the primary sense by which neonatal mice form social memories. Data from our lab indicate that mouse pups as early as postnatal day (P) 3 can distinguish between their caregiving mother and a

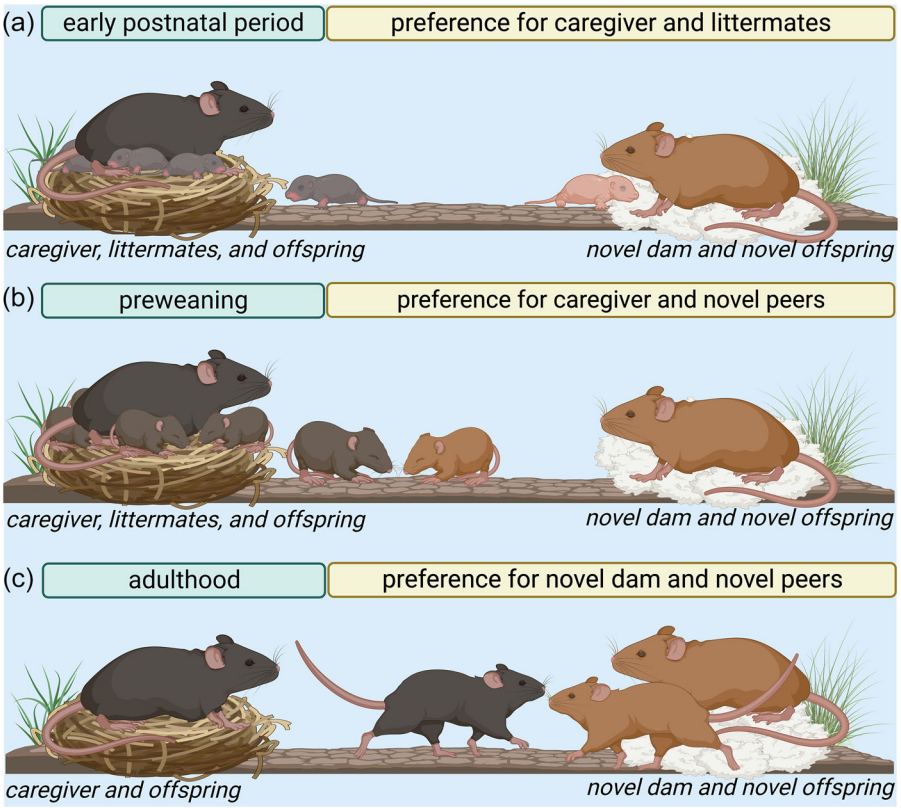

FIGURE 1 Social preference throughout development. (a) In the early postnatal period, mouse pups prefer their caregiving mother over a novel dam as well as their littermates over novel peers. (b) Before weaning, mouse pups prefer a novel peer over a littermate but retain preference for their caregiving mother over a novel dam. (c) In adulthood, mice prefer both novel peers over familiar peers and novel dams over their caregiving mother.

novel dam, even when physical contact is prevented (Laham et al., 2021), making it likely that gustatory and somatosensory inputs are not necessary for memory retrieval. During this time and through weaning, mouse pups prefer the caregiving mother (Figure 1) (Laham et al., 2021; Mogi et al., 2017). Throughout maturation and into adulthood, mice retain the ability to discriminate between their caregiving mother and a novel mother, but now show a strong social novelty preference whereby more time is spent investigating a novel mother (Figure 1) (Laham et al., 2021; Mogi et al., 2017). Many months after physical separation at weaning, adult offspring show evidence of a persistent memory of their caregiving mother, and this memory manifests itself as a diminished preference for her in favor of a novel dam (Laham et al., 2021). As is the case with caregiver recognition, rodents are able to identify siblings during the early postnatal period and into adulthood (Clemens & Brecht, 2021; Clemens et al., 2020; de León Reyes et al., 2022; Hepper, 1986). In most of these reports, social recognition for kin manifests itself as a preference for kin over novel conspecifics up until the end of the second postnatal week of life, after which the preference switches to novel conspecifics over kin.

Evidence suggests that the earliest social memories can begin in utero (Hepper, 1986), although postnatal experience alone is sufficient to form the association as cross-fostered mouse pups form comparably robust memories for their unrelated caregiving mothers (Laham et al., 2021) and siblings (Hepper, 1986). Some evidence suggests that several mouse strains can use olfactory cues to detect genetically related individuals regardless of familiarity. In a laboratory choice test, adult female wild-stock house mice prefer to nest with genetically related littermates compared to novel unrelated females, regardless of whether the mice cohabit with one another or have been separated since weaning (Green et al., 2015). Since adult mice typically demonstrate preference for novel mice over their littermates, these results are surprising. However, this unexpected familiarity preference may be related to the cooperative breeding strategy shown by this species. It should be noted that most other rodent social preference studies measure time spent investigating as the main dependent measure, not choice of nesting, huddling, or sleeping.

2.2 | Emerging preference for novel peers

It is perhaps not surprising that rodents demonstrate an initial preference for their littermates given that they live together in the nest during early life, where mouse pups receive

nourishment and protection from the mother. This prolonged exposure allows for robust and lasting memories of littermates and mother to form. However, for both mice and rats, preference for novel peers over littermates begins to emerge around the end of the second postnatal week (Clemens & Brecht, 2021; Clemens et al., 2020; de León Reyes et al., 2022; Diethorn & Gould, 2023; Hepper, 1986). Although mouse pups continue to prefer their caregiving mother over a novel dam at this age (Laham et al., 2021), we found that the same is not true for littermates, with pups preferring novel pups over familiar littermates (Figure 1) (Diethorn & Gould, 2023). The continued preference for the caregiving mother over a novel dam despite an emerging preference for novel peers over littermates during this time seems adaptive as the end of the second postnatal week of life is a time when pups still rely on the mother for nourishment and protection, but are becoming more mobile and beginning to venture from the nest in the wild (Vestal et al., 1980).

In addition to forming and retrieving memories of littermates and discriminating between them and novel peers around the end of the second postnatal week, mouse pups show evidence of forming short-term memories of previously unencountered peers around this time. After just 5 minutes of interaction with an age- and sex-matched pup, P14 mouse pups exhibit decreased investigation time after a subsequent encounter 1 hour later. These results suggest the capacity to form new social memories after a brief encounter begins around the end of the second postnatal week, a phenomenon that is noted by higher investigation times for novel versus recently encountered peers (Diethorn & Gould, 2023). At P14, however, social novelty preference is not observed in all mice. The preference for novel peers becomes more common with age such that, by P21, the percent of mice that prefer a novel conspecific over a familiar has increased nearly twofold compared to P14. By young adulthood, virtually all mice show this preference (Diethorn & Gould, 2023), although very infrequently, an adult control mouse exhibits a familiarity social preference (Cope et al., 2020; Laham et al., 2021; Lopez-Rojas et al., 2022; Wu et al., 2021). While social novelty preference for peers is normal in most rodent species, prairie voles notably show a strong familiarity preference for partners of either sex (Beery et al., 2018).

It is important to recognize that the type of behavioral paradigm used may influence the time in development when social discrimination abilities can be detected. That is, if mature social memory develops gradually, a more difficult task may produce a completely negative result at a young age, even though more basic capabilities exist. For example, a previous study found no evidence of social memory for recently encountered conspecifics in P28 mice despite consecutive presentations (Domínguez et al., 2019). The lack of evidence in this study may be due to the use of a behavioral paradigm that presents the stimulus mouse in a small cage within the testing apparatus, instead of allowing direct social interaction via physical contact.

2.3 | The role of the CA2 in developmental social memory

Despite strong evidence of changes in social memory as mice transition from preference for the mother and littermates to preference for the mother and novel peers, to an overall preference for novelty, numerous studies suggest that the CA2 region participates in all of these types of social discrimination. Chemogenetic silencing of the CA2 in mice as young as P10 prevents the ability to discriminate between the caregiving mother and a novel dam (Laham et al., 2021). Despite the change from preferring the caregiving mother to the novel mother that occurs after weaning in mice, the CA2 remains important in social discrimination (Laham et al., 2021). Likewise, the ability to discriminate between novel and recently encountered peers requires the CA2 as early as P14 in mice, with chemogenetic silencing at this age abolishing diminished investigation for a previously encountered peer (Diethorn & Gould, 2023). CA2 involvement in this type of social discrimination continues well into adulthood (Laham et al., 2021), including the ability to recognize a littermate and prefer a novel social stimulus (Hitti & Siegelbaum, 2014). Although the CA2 appears to be central to social discrimination throughout life, the molecular and cellular development of this region likely contributes to some of the associated behavioral changes that occur with time.

3 | POSTNATAL DEVELOPMENT OF THE INTRINSIC CA2 PROFILE

The unusual properties of the CA2, including the molecular profile of its pyramidal cells and the circuitry that these cells engage with, have been well-characterized in adult rodents using numerous methods. However, due to technical limitations of working with neonatal animals, our understanding of how this region forms remains unclear. Below, we discuss what is currently known about how the CA2 arises in developing mammals and when its unique properties begin to emerge and set it apart from the neighboring CA fields.

3.1 | Early development of CA2 structure

The pyramidal cell layer of the CA2 appears to be a hippocampal subregion that forms early in mammalian embryonic development. Arising from the walls of the lateral ventricles, newborn neurons destined to become pyramidal cells migrate across the hippocampal rudiment to form the pyramidal cell

layer (Angevine, 1965; Bayer, 1980). In mice, birth-dating studies have shown that the production of pyramidal cells begins around embryonic day (E) 10, with a coalesced pyramidal cell layer becoming evident around E15. Similar to the neocortex, the hippocampal pyramidal cell layer forms in an inside-out direction with younger cells migrating past older ones (Angevine, 1965; Bayer, 1980). Pyramidal cells of the CA1 and CA3 begin to form around the same time as those in the CA2, but their production extends a few days longer, to E18, and dentate gyrus development continues throughout postnatal life (Angevine, 1965). In nonhuman primates, CA2 pyramidal cell formation begins during early gestation (around E38), the same time as other hippocampal subfields, but, as is the case in mice, is the first to complete formation, by E56 (Rakic & Nowakowski, 1981). These findings suggest that the production of pyramidal cells in the CA2 may be completed earlier than in the adjacent CA fields, but it should be noted that the much smaller size of the CA2 and the small number of animals used for these ^{3}H-thymidine labeling studies may have biased against finding labeled neurons at later embryonic time points.

Inhibitory interneurons of the hippocampal CA fields are known to originate from the medial and caudal ganglionic eminences (Li & Pleasure, 2014). In the mouse, the first inhibitory interneurons are born on E9, but their migratory paths are longer than those of principal neurons and they do not invade the hippocampus until about E14 (Tricoire et al., 2011). During mouse embryonic development, migration of interneurons from the medial ganglionic eminence to the CA2 reaches its peak by E18, several days after pyramidal cells populate the region, before significantly dropping in number during the early postnatal period (Katahira et al., 2018; Tricoire et al., 2011). In the macaque CA2, the first interneurons expressing parvalbumin (PV) can be observed in the pyramidal layer around E88 (Berger et al., 1999), although the birthdate of these neurons remains unknown. The CA2 has a high number of PV+ interneurons relative to the CA1 and CA3 (Botcher et al., 2014), and this regional difference becomes evident as early as P10 in mice (Lopez-Tellez et al., 2004). By P17 in mice, the CA2 region has nearly twice the number of PV+ interneurons as the CA1 and CA3 (Domínguez et al., 2019). PV+ interneurons are known to induce sustained iLTD, a form of plasticity that facilitates emerging social recognition abilities (Domínguez et al., 2019; Piskorowski et al., 2016). Similarly, ITDP in CA2 evoked by simultaneous innervation from the entorhinal cortex and CA3 is also mediated by PV+ interneurons and is reduced following interaction with a novel conspecific (Leroy et al., 2017).

Once neurogenesis and neuronal migration have occurred, genesis of astrocytes and microglia continues in the postnatal period (Kitamura et al., 1984). As with other brain regions, full maturity of the CA2 involves dendritic development and synaptogenesis, as well as associated regressive events, such as dendritic retraction and synapse elimination. Although no studies have examined these processes directly in the developing CA2, indirect measures of maturity suggest that the CA2 may have a slightly accelerated developmental profile relative to the CA1 and CA3. For example, the overall volume of the CA2 in monkeys and humans is closer to adult size than the adjacent CA fields around the time of birth (Jabès et al., 2011; Lavenex & Lavenex, 2013), with CA2 pyramidal cells possessing 30% larger soma than CA3 pyramidal cells in 1-month-old human infants (Zaidel, 1999), a difference that does not exist in adulthood. Taken together with ^{3}H-thymidine birth-dating studies on CA2 pyramidal cells, these findings suggest that the CA2 may reach maturity relatively early; however, it should be noted that other developmental processes, such as cell death, appear to occur simultaneously in CA1, CA2, and CA3 (Mosley et al., 2017).

Although the basic time frame and trajectory of CA2 formation is not altogether dissimilar from that of the other CA fields, the CA2 differs markedly from these areas in terms of gene expression. A growing body of evidence suggests that many of the molecules present in high concentrations in the CA2 are plasticity modulators that contribute to its electrophysiological properties and behavioral function.

3.2 | Developmental expression of CA2 molecular markers and their roles in plasticity

In adult rodents, the CA2 can be identified by the presence of a number of molecular markers, some of which contribute to its unique cellular properties (Table 1; Figure 2) (Carstens et al., 2016; Farris et al., 2019; Gerber et al., 2019; Kohara et al., 2014). Pyramidal cells in the CA2 of humans, nonhuman primates, and rodents express regular of G-coupled protein 14 (RGS14), a scaffolding protein with a strong influence over synaptic plasticity. RGS14 orchestrates the assembly of protein cascades connecting cell surface receptors to intracellular space, contributing to plasticity resistance (Evans et al., 2018; Lee et al., 2010; Squires et al., 2018). RGS14 first appears in the mouse CA2 and other parts of the hippocampus on P7 (Evans et al., 2014), with data from our lab and others showing localized expression of this marker by the second postnatal week that continues to strengthen with age (Figure 2) (Diethorn & Gould, 2023; Laham et al., 2021). Purkinje cell protein 4 (PCP4), which mediates calcium binding through calmodulin, is also highly expressed in the rodent CA2 in adulthood as well as in early postnatal development, with expression localized to the CA2 by P14 in one study and by P21 in another (Figure 2) (Laham et al., 2021; San Antonio et al., 2014).

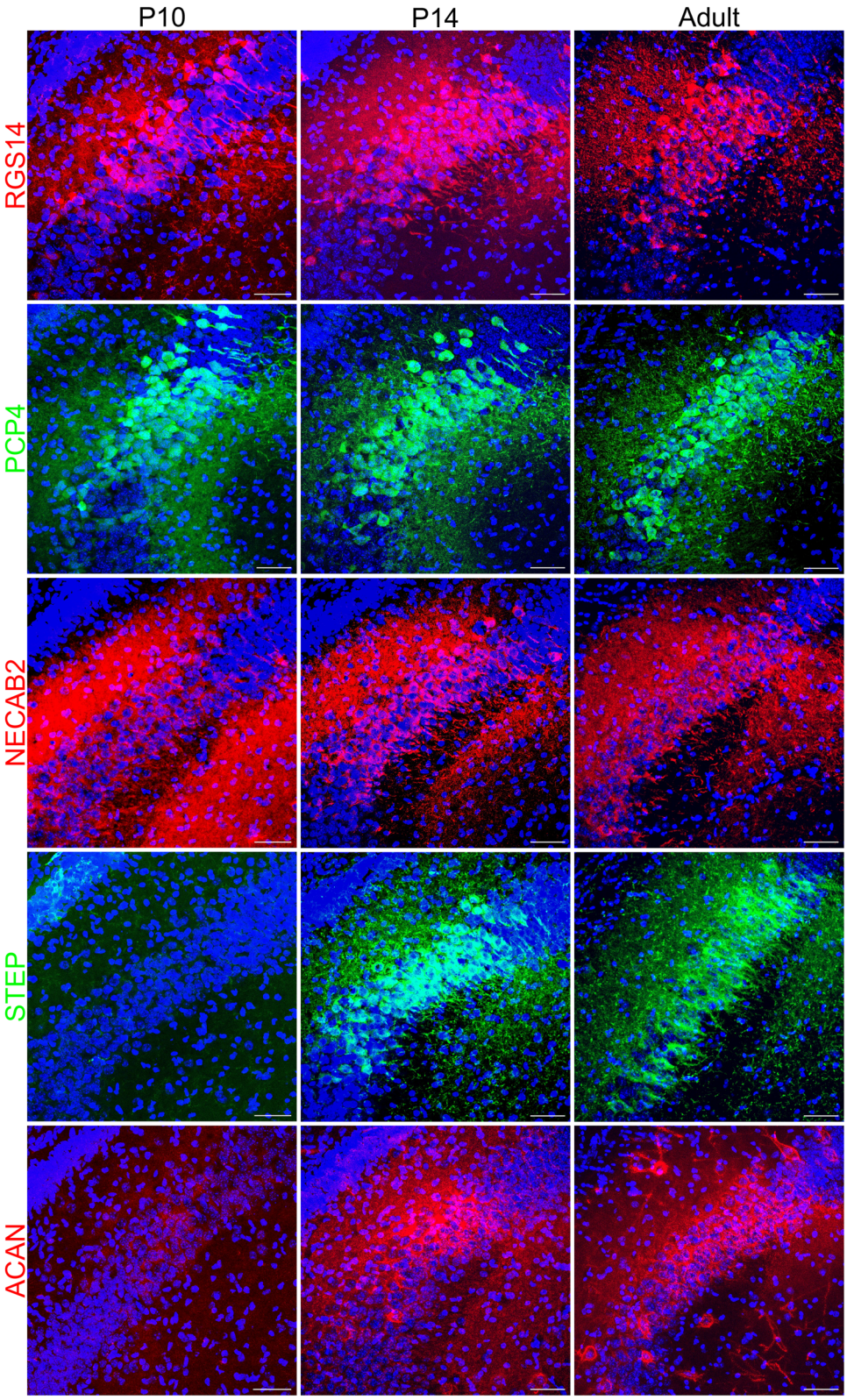

FIGURE 2 Developmental expression of CA2 markers in C57BL6/J mice. Left: Confocal images from postnatal day (P) 10 pups showing robust immunohistochemical expression of regulator of G protein signaling 14 (RGS14), Purkinje cell protein 4 (PCP4), and neuronal Ca^{2+}-binding protein 2 (NECAB2) in dorsal CA2. Little to no expression of striatal-enriched protein tyrosine phosphatase (STEP) and aggrecan (ACAN) is present at this age. Middle: Confocal images from P14 pups showing immunohistochemical expression of RGS14, PCP4, NECAB2, STEP, and ACAN in dorsal CA2. All markers show roughly adult-like staining in CA2 at this age. Right: Confocal images from adult mice showing immunohistochemical expression of RGS14, PCP4, NECAB2, STEP, and ACAN in dorsal CA2. Scale bars = 50 μm. All sections were counterstained with Hoechst 33342. See Diethorn and Gould (2023) for histological methods.

TABLE 1 Developmental appearance of CA2 markers in rodents.

Marker	First CA2 appearance	General function	CA2 function	References
RGS14	P7	Synaptic scaffolding	Restricts plasticity	Evans et al., 2014
PCP4	P4	Calcium binding	Restricts plasticity	San Antonio et al., 2014
NECAB2	P3	Calcium binding	Restricts plasticity	Sugita et al., 2002
STEP	P7	Glutamate regulator	Diminishes synaptic strength, involved in memory	Blázquez et al., 2019; Cases et al., 2018
A1R	P7	Synaptic vesicle release	Reduces synaptic vesicle release	Oshiishi et al., 1999
MR	P3	Adrenal steroid receptor	Adrenal steroid binding, gene expression initiation	McCann et al., 2021
ACAN	P5	PNN component	Restricts plasticity	Noguchi et al., 2017

Abbreviations: A1R, adenosine A1 receptor; ACAN, aggrecan; MR, mineralocorticoid receptor; NECAB2, neuronal Ca^{2+}-binding protein 2; PCP4, Purkinje cell protein 4; RGS14, regulator of G protein signaling 14; STEP, striatal-enriched protein tyrosine phosphatase.

The neuronal calcium binding protein, NECAB2, is preferentially expressed in hippocampal CA2 of adult mice and, according to our findings, useful for identifying the CA2 as early as P3, though restriction of this marker to the CA2 occurs around P10 (Figure 2) (Laham et al., 2021; McCann et al., 2021; Zimmermann et al., 2013). Striatal-enriched protein tyrosine phosphatase (STEP), also called Ptpn5, diminishes synaptic strength by regulating glutamatergic receptors and is also enriched in the rodent CA2 compared to neighboring CA1 and CA3 (Boulanger et al., 1995). Importantly, the absence of STEP has been associated with impairments in both social and nonsocial memory (Blázquez et al., 2019). No literature exists on the postnatal appearance of STEP in the CA2 specifically, but the hippocampus in general expresses adult-like levels of STEP at P7 (Cases et al., 2018). Additionally, data from our lab indicate that, in addition to RGS14, PCP4, and NECAB2, STEP is also localized to the mouse CA2 by P14 (Figure 2). Similarly, adenosine 1A receptors (A1Rs) are also enriched in the CA2 and reduce synaptic vesicle release, contributing to diminished synaptic transmission in this region. A1Rs are detectable as early as P7 in rodents, though characteristic peak expression delineating CA2 from neighboring CA1 and CA3 does not appear until P28 (Caruana & Dudek, 2020; Oshiishi et al., 1999).

The CA2 is also highly enriched in mineralocorticoid receptors (MRs), which have a high affinity for glucocorticoids, as well as for mineralocorticoids, such as aldosterone. MR expression begins in the CA2 during embryonic life where it is synthesized primarily by pyramidal cells. As early as P3, differential expression of MR can be observed in the CA2 compared to neighboring CA1 and CA3 (McCann et al., 2021). This pattern of expression persists into adulthood (Lawson et al., 1991; McCann et al., 2021). The early expression of MR seems to serve as an initiator for the unusual pattern of gene expression observed in the CA2. Embryonic deletion of MR reduces expression of NECAB2 and RGS14 while also increasing expression of genes that are more commonly expressed in CA1 (McCann et al., 2021). MR control over these genes continues into adulthood as conditional CA2 deletions produce these effects in adult mice. Furthermore, activation of these receptors is required for CA2-specific gene expression, as MR antagonist treatment produces the same effects (McCann et al., 2021). Along with the reduction in NECAB2 and RGS14 expression, MR deletion renders CA2 susceptible to LTP under conditions that are known to elicit it in the CA1 (McCann et al., 2021). Importantly, MR deletion also impairs social memory in adulthood (McCann et al., 2021), suggesting that MR activation sets in motion gene expression patterns that modulate synaptic plasticity in a way that is conducive to social memory.

3.3 | Perineuronal nets are concentrated in the developing CA2

In addition to its unusual gene expression characteristics, the CA2 is distinct in its high concentration of perineuronal nets (PNNs), extracellular matrix structures that are known to regulate plasticity. In the CA2, PNNs envelop both PV-expressing interneurons as well as pyramidal cells (Sorg et al., 2016). PNNs are composed of chondroitin sulfate proteoglycans (CSPGs) with changing sulfation patterns as animals develop and age (Laham & Gould, 2022). Aggrecan, the main neuronal CSPG, is localized to the CA2 as early as P5 and becomes adult-like in appearance by P14 (Table 1; Figure 2) (Noguchi et al., 2017). Labeling of PNNs with the plant lectin Wisteria floribunda agglutinin delineates CA2 PNNs beginning around P10, with more concentrated PNNs surrounding pyramidal cells observed by P14 (Horii-Hayashi et al., 2015; Laham et al., 2021). In the developing CA2, PNNs seem to be influenced by experience, with one study showing enhanced PNNs at P21 in response to rearing in an enriched environment (Carstens et al., 2016).

PNNs contribute to synaptic plasticity resistance in the CA2. After degradation with the enzyme chondroitinase ABC, P14–P18 CA2 pyramidal cells exhibit LTP at

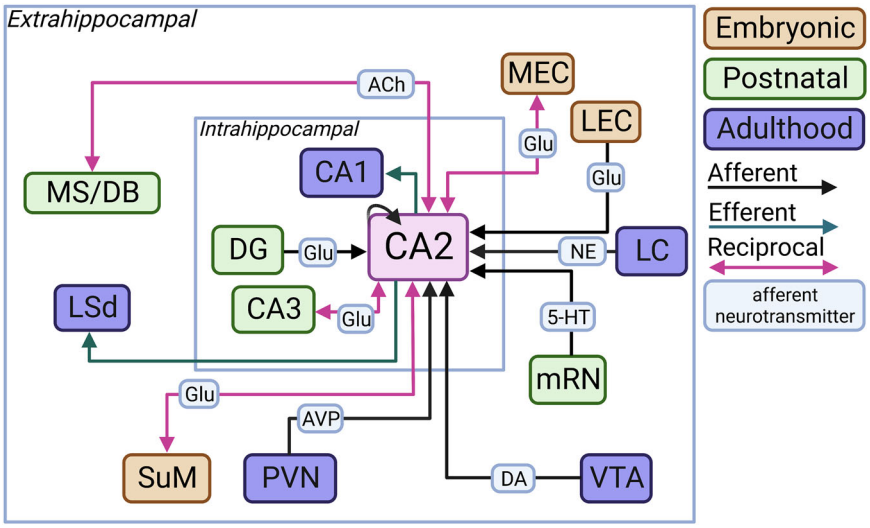

FIGURE 3 CA2 connectivity throughout development. Diagram of known afferent and efferent CA2 projections and their earliest known appearance. Regions in orange are known to be connected to the CA2 during the embryonic period and those in green are connected to the CA2 during the early postnatal period, although possibly earlier. Those labeled in blue are known to be connected to CA2 in adulthood, but have not been investigated for their appearance during development. MS/DB, medial septum/diagonal band of Broca; LSd, dorsal lateral septum; SuM, supramammillary nucleus; PVN, paraventricular nucleus; VTA, ventral tegmental area; mRN, median raphe nucleus; LC, locus coeruleus; MEC/LEC, medial/lateral entorhinal cortex; DG, dentate gyrus; Glu, glutamate; ACh, acetylcholine; AVP, vasopressin; DA, dopamine; NE, norepinephrine; 5-HT, 5-hydroxytryptamine or serotonin.

excitatory synapses that is typically suppressed at this age (Carstens et al., 2016). The appearance of PNNs in other brain regions has been associated with the closure of critical periods of plasticity. Since we and others have shown that PNNs are enriched specifically in the CA2 by P14, their appearance, along with increased expression of RGS14, PCP4, NECAB2, and STEP, may indicate the closure of a CA2 plasticity period. Evidence suggests that CA2 PNNs are important for social recognition in adulthood as their degradation impairs this ability (Carstens et al., 2021; Cope et al., 2020; Domínguez et al., 2019). In addition, excessive CA2 PNNs can also interfere with social memory in mice (Cope et al., 2020), suggesting the presence of an inverted-U relationship where optimal levels of CA2 PNNs facilitate social discrimination abilities. The involvement of PNNs in the emergence of developmental social memory remains unexplored. Since the ability to discriminate between familiar and novel dams is detectable as early as P3 (Laham et al., 2021), a time when PNNs are not present in the CA2, it seems highly unlikely that they are necessary for this function. However, CA2 PNNs become substantial around the time when novelty preference prevails (Laham et al., 2021) and when pups become able to form short-term memories of recently encountered conspecifics (Diethorn & Gould, 2023), suggesting that their appearance is important for emerging social capabilities.

4 | DEVELOPMENT OF CA2 CONNECTIVITY

While the CA2 is known to be a highly interconnected region in adulthood, receiving innervation from more than 10 distinct intra- and extrahippocampal subregions (Figure 3), not including recurrent connections to itself, and sending projections to the dorsal/ventral CA1, supramammillary nucleus (SuM), septal nuclei, diagonal bands of Broca, and the medial entorhinal cortex (Cui et al., 2013; Leroy et al., 2018; Lopez-Rojas et al., 2022; Martig & Mizumori, 2011; Rowland et al., 2013; Wagatsuma et al., 2018), research characterizing the first appearance of these projections during development is limited. In this section, we review what is known about pre- and postnatal development of afferent and efferent CA2 connectivity.

4.1 | Extrahippocampal connectivity

Afferents from the SuM of the hypothalamus to the CA2 have been observed during primate fetal life, with innervating terminals seen as early as E109 in monkeys and by 20 weeks gestation in humans (Berger et al., 2001). Although this projection arises in embryonic development, it undergoes further innervation during the postnatal period of both monkeys and humans (Berger et al., 2001). To date, no studies have investigated the presence of SuM afferents in the CA2 during embryonic life in rodents, but we have shown that this pathway is present by P14 in mouse pups and continues to develop during the late postnatal period (Diethorn & Gould, 2023). The appearance of the SuM to CA2 projection in embryonic development is in part mediated by CA2 MR activation, with conditional receptor deletion resulting in profoundly diminished and sometimes a complete absence of glutamatergic SuM innervation in postnatal life (McCann et al., 2021). Importantly, the SuM to CA2 projection contains specific information regarding social novelty in adult mice (Chen et al., 2020), and additional hypothalamic projections

contain oxytocin and vasopressin, neuropeptides that have enriched receptors in CA2 and facilitate social recognition (Piskorowski & Chevaleyre, 2018).

Similarly, projections from the lateral entorhinal cortex to the CA2 are known to convey information on social stimuli in adult animals (Lopez-Rojas et al., 2022) and arise during embryonic development of humans (Hevner & Kinney, 1996). The CA2 also receives projections from the medial entorhinal cortex, and tracing studies indicate that this projection also arises in embryonic development, with innervating fibers seen in the CA2 around E18 in rodents (Borrell et al., 1999; Supèr & Soriano, 1994). While the CA2 was not analyzed as a distinct region of the hippocampus, one report described cholinergic fibers emanating from the medial septal nucleus/diagonal band of Broca throughout the entire dorsal hippocampus as early as P0 in rat pups that reached adult-like levels by P32 (Aznavour et al., 2005).

Using retrograde tracing, we observed that, by P14, the CA2 receives innervation from the median raphe nucleus, the entorhinal cortex, and the dentate gyrus (Diethorn & Gould, 2023). Unfortunately, however, technical limitations have made it difficult to explore the early development of these projections in neonatal animals. For this reason, available evidence is lacking on the earlier origins of these connections, as well as when inputs from other known afferent regions, like the paraventricular nucleus and the medial and lateral septal nuclei, first form in development (Cui et al., 2013). Similarly, no data exist on the formation of known efferents from the CA2 to the medial and lateral septal nuclei, the diagonal bands of Broca, the SuM, and the medial entorhinal cortex (Cui et al., 2013; Rowland et al., 2013).

4.2 | Intrahippocampal connectivity

The intrahippocampal commissural projection arising from the CA3 and projecting to both ipsilateral and contralateral CA2 is present by P1 in mouse pups and sends detectable excitatory innervation to CA2 pyramidal cells by P7 (Borrell et al., 1999; San Antonio et al., 2014). The CA2 has reciprocal projections with the CA3, but the developmental appearance of these projections is unknown. Using retrograde tracing in mice, we found that, by P14, the CA2 receives ample innervation from the dentate gyrus (Diethorn & Gould, 2023), a pathway that is continually rejuvenated by the addition of postnatally generated granule cells to this circuit (Llorens-Martín et al., 2015). Others have shown that recurrent CA2 projections exist during development, appearing as early as P18, though the number of synaptically connected pyramidal cells is sparse at this time (Okamoto & Ikegaya, 2019). Expression of semaphorin 7A, an unusual member of the semaphorin family due to its promotion of axon growth, also peaks in the CA2 around this time and perhaps is facilitating innervation of axons from afferent regions (Pasterkamp et al., 2007). Along these lines, it is likely relevant that axon-promoting and repelling molecules have been known to be sequestered by PNNs (Wang & Fawcett, 2012), which may work together to guide incoming axons into the nascent CA2. While the CA2 sends ample projections to both dorsal and ventral CA1, with the latter projection being implicated in social memory (Meira et al., 2018), no data exist on the earliest formation of these projections in development.

5 | DISCUSSION

To date, considerable efforts have been made to elucidate the morphology, connectivity, and behavioral contributions of the hippocampal CA2 subregion in mammals. We now know that the CA2 is integral to social behaviors, made possible by its extrahippocampal and intrahippocampal connectivity as well as by intrinsic properties that heavily limit plasticity and likely promote sparse activation of pyramidal cells. Most knowledge generated by the field has been collected from adult animals, in part due to limitations in neuroscientific techniques available for developmental rodent research, including the lack of tractable behavioral measures for altricial animals. Together, these constraints have hindered rigorous analysis of neonatal brain development and how this development contributes to discrete behaviors. In this review, we aggregated what is currently known about the developing CA2, including the role it plays in early social memories for kin and unrelated conspecifics, the nature and origin of excitatory and inhibitory cells, the appearance of characteristic markers that contribute to limited plasticity, and the connections present in the CA2 at this time.

It is clear that the basic formation of the CA2 occurs relatively early in rodents, monkeys, and humans. Both pyramidal cells and interneurons in this region migrate to their final destinations rapidly prior to birth. Also prior to birth, key inputs from the SuM and the entorhinal cortex are present in the primate CA2. Soon after birth, the CA2 begins to express some of its characteristic markers that distinguish it from neighboring CA1 and CA3 and contribute to its unique molecular profile. By P14, at least six different receptors and proteins are highly expressed in CA2 pyramidal cells. The first to appear are MRs, which are present by P3 in rodents and seem to initiate production of both RGS14 and NECAB2, two more CA2 markers that restrict plasticity and are localized to the CA2 by P7 and P10, respectively. Around the same time, additional markers like STEP and PCP4 concentrate in CA2 pyramidal cells along with A1Rs on the surface of these cells. These markers, along with the presence of dense PNNs around both excitatory pyramidal cells and inhibitory interneurons, become adult-like in appearance around P14, when the CA2 is

receiving ample innervation from the SuM, the dentate gyrus, and the entorhinal cortex.

During the second postnatal week in rodents, when the aforementioned CA2 projections and cellular properties near their adult-like state, social recognition abilities and preference for novel social stimuli begin to emerge in pups. While rodents and primates undoubtedly form rudimentary social memories for caregivers and kin soon after birth, likely facilitated by both prolonged exposure to these social stimuli and the embryonic development of innervation to the CA2 from the SuM and the entorhinal cortex, the elaboration of these abilities and the switch in preference from familiar to novel conspecifics that is detectable around P14 is probably facilitated by the coincident appearance of these CA2 characteristics. Subsequent development of the CA2 that occurs after this point, including projections from the SuM and the dentate gyrus (Diethorn & Gould, 2023), may point to an expansion of social memory capabilities with age. To date, however, these specific projections have not been interrogated in the CA2 across development.

Given that neuropsychiatric disorders with social communication and interaction deficits primarily manifest in early development, a thorough understanding of the healthy neural development of brain regions key to social behavior may be useful in pinpointing therapeutic targets. Children with Phelan–McDermid syndrome and Fragile X syndrome experience difficulty recognizing familiar social stimuli, and deficits in social interactions experienced by these individuals can manifest as early as 2–3 years of age (Gray & Tonge, 2001; Guillory et al., 2021; Holsen et al., 2008; Williams et al., 2013). Children with other conditions related to autism spectrum disorders, like 22q11 deletion syndrome, develop social cognition deficits slightly later in life, beginning around age 6 (Kiley-Brabeck & Sobin, 2006). Research suggests that interventions implemented early in life may be more beneficial than those started on older children (Zwaigenbaum et al., 2015). These data indicate that a better understanding of neural mechanisms underlying the emergence of healthy social behavior is an important step in the development of effective interventions for children with social interaction deficits. For this reason, additional research on the development of hippocampal CA2 structure and function during the early postnatal period in both healthy animals and in models of social dysfunction may be integral to both our understanding of and our ability to treat neurodevelopmental disorders.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Emma J. Diethorn https://orcid.org/0000-0002-9859-2440
Elizabeth Gould https://orcid.org/0000-0002-8358-0236

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