

NEUROGENESIS

Pregnancy-responsive pools of adult neural stem cells for transient neurogenesis in mothers

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Adult neural stem cells (NSCs) contribute to lifelong brain plasticity. In the adult mouse ventricular-subventricular zone, NSCs are heterogeneous and, depending on their location in the niche, give rise to different subtypes of olfactory bulb (OB) interneurons. Here, we show that multiple regionally distinct NSCs, including domains that are usually quiescent, are recruited on different gestation days during pregnancy. Synchronized activation of these adult NSC pools generates transient waves of short-lived OB interneurons, especially in layers with less neurogenesis under homeostasis. Using spatial transcriptomics, we identified molecular markers of pregnancy-associated interneurons and showed that some subsets are temporarily needed for own pup recognition. Thus, pregnancy triggers transient yet behaviorally relevant neurogenesis, highlighting the physiological relevance of adult stem cell heterogeneity.

Stem cells in the adult mouse brain dynamically integrate and respond to environmental signals throughout life (1, 2). Ventricular-subventricular zone (V-SVZ) neural stem cells (NSCs) residing along the lateral ventricles are radial glial fibrillary acidic protein (GFAP)-expressing cells and exist in quiescent or activated states (2). NSCs in distinct spatial domains of the V-SVZ give rise to different subtypes of olfactory bulb (OB) interneurons (2). Once integrated, adult-born neurons tend to persist long term (3, 4). In addition to constitutive neurogenesis, regionally distinct adult NSCs can be modulated by physiological states such as hunger and satiety (5). However, whether other physiological states dynamically control distinct pools of adult stem cells and what is the functional relevance of on-demand stem cell recruitment for adaptive brain plasticity remain to be fully elucidated.

Pregnancy induces major structural changes in multiple brain regions in preparation for motherhood and parental care (6). In mice, proliferation in the adult V-SVZ increases at gestation day (Gd) 7 and again at postpartum day (Ppd) 7 (7, 8), and newborn neuron dendritic complexity and synaptic integration are enhanced in mothers (9, 10). Perturbing adult V-SVZ neurogenesis sometimes results in defects in maternal behavior depending on the timing of stem cell manipulation (7, 8, 10–12). Here, we investigated whether spatial and temporal control of distinct stem cell pools occurs in response to pregnancy to generate specific OB interneuron subtypes, which differentially affect olfactory behavior during motherhood. Different physiological states may therefore regulate regionally distinct stem cell

pools, revealing a functional map of adult NSC heterogeneity in the V-SVZ.

Recruitment of regionally distinct NSCs during pregnancy

We first quantified NSC proliferation (GFAP⁺ Ki67⁺) on several different days of gestation and at Ppd 7.5 (Fig. 1A). Pregnancy did not uniformly enhance NSC proliferation in the V-SVZ. Instead, NSC subpopulations in domains that tend to be more quiescent under homeostasis, such as the ventromedial wall (Fig. 1, B to D), the roof (Fig. 1, B and F, and fig. S1, A and C), and the dorsomedial corner (fig. S1, A and B), were active. By contrast, only some stem cell pools residing in more proliferative V-SVZ domains, such as the ventrolateral wall (Fig. 1, B, C, and E) and dorsolateral wedge (Fig. 1, B and G, and fig. S1C), responded to pregnancy, but not those in the dorsolateral and intermediate V-SVZ (fig. S1, A, D, and E). In addition to the spatial pattern of recruitment, pregnancy-related domains displayed distinct temporal dynamics (Fig. 1H). Dividing NSCs in the roof and the ventral V-SVZ increased at Gd 4.5 and 7.5, respectively (Fig. 1, D to F). Conversely, in the dorsolateral wedge and in the dorsomedial corner, NSC proliferation increased on several gestation days (Fig. 1G and fig. S1B). All changes were transient and mostly occurred during the first week of gestation, except in the dorsolateral wedge (Fig. 1G).

To visualize proliferation dynamics throughout the V-SVZ, we analyzed whole-mount preparations of the medial and lateral walls for MCM2. Density maps confirmed the temporal recruitment of regionally distinct domains on different gestation days (Fig. 1I and figs. S2F and S3F) and revealed increased proliferation in more caudal regions in both the medial (fig. S2) and lateral (fig. S3) walls, which are less proliferative in virgins. Pseudopregnant female mice, which have a similar neuroendocrine response to early pregnancy, shared

only some dividing regions in the lateral wall with pregnant females (fig. S4, A and B). In the medial wall, increased proliferation was only observed in pregnant females (fig. S4, C and D), suggesting that the medial V-SVZ, as well as some regions in the lateral wall, are selectively responsive to pregnancy. Thus, regionally distinct stem cells can be transiently recruited in response to different physiological states.

Pregnancy-associated interneurons are transient

Most adult-born neurons integrate into the granule cell layer (GCL) of the main olfactory bulb (MOB), with a bias toward the deep GCL (13), the connectivity of which differs from the superficial GCL (14). Some interneurons are also added to the glomerular layer (GL) (1), but very rarely to the mitral cell layer (MCL) (15). Adult-born neurons are functionally integrated 2 to 3 weeks after their generation (3, 16). To investigate whether the recruitment of spatially distinct NSCs during pregnancy results in the addition of specific OB interneuron subtypes in mothers, we pulsed pregnant female mice once with a thymidine analog on different gestation days (Gd 0.5, 2.5, 4.5, or 7.5) and analyzed their OBs 20 days later, coinciding with the time of birth and early perinatal care (Fig. 2, A and B). The distribution of analog⁺ neurons within OB layers differed depending on their day of birth (fig. S5, A and B). The MCL was the only layer in which an increase in new neurons (thymidine analog⁺ NeuN⁺) born on Gd 0.5 and 2.5 occurred (Fig. 2, C to F and I). In the GCL, only newborn neurons labeled at Gd 4.5 and 7.5 were increased in mothers (Fig. 2, C to F, I, and fig. S5C), largely due to incorporation into the superficial GCL (fig. S5D). Therefore, pregnancy-related neurogenesis increases in sublayers where fewer new neurons integrate under homeostasis. In the accessory olfactory bulb (AOB) (Fig. 2, B to F), where adult-born neurons are implicated in reproductive social behavior (17–20), only GCL neurons generated on Gd 4.5 and 7.5 increased (fig. S5, E and F). Pregnancy-associated interneurons were functionally integrated into existing OB circuitry, as measured by c-fos expression (fig. S6, A to D). In the MOB of perinatal mothers [20 days post-analog injection (dpi)], the increase in c-fos⁺ analog⁺ cells was restricted to the superficial GCL and MCL (fig. S6, B and C), underscoring the importance of pregnancy-associated neurogenesis in these two layers in early motherhood.

To investigate whether pregnancy-related interneurons are transient or long-lasting, we assessed their survival 10 days later (30 dpi), around periweaning, when pups are increasingly feeding on solid food and mothers are less engaged in maternal care (Fig. 2A). In all layers in which neurogenesis was enhanced in perinatal mothers, the number of newborn

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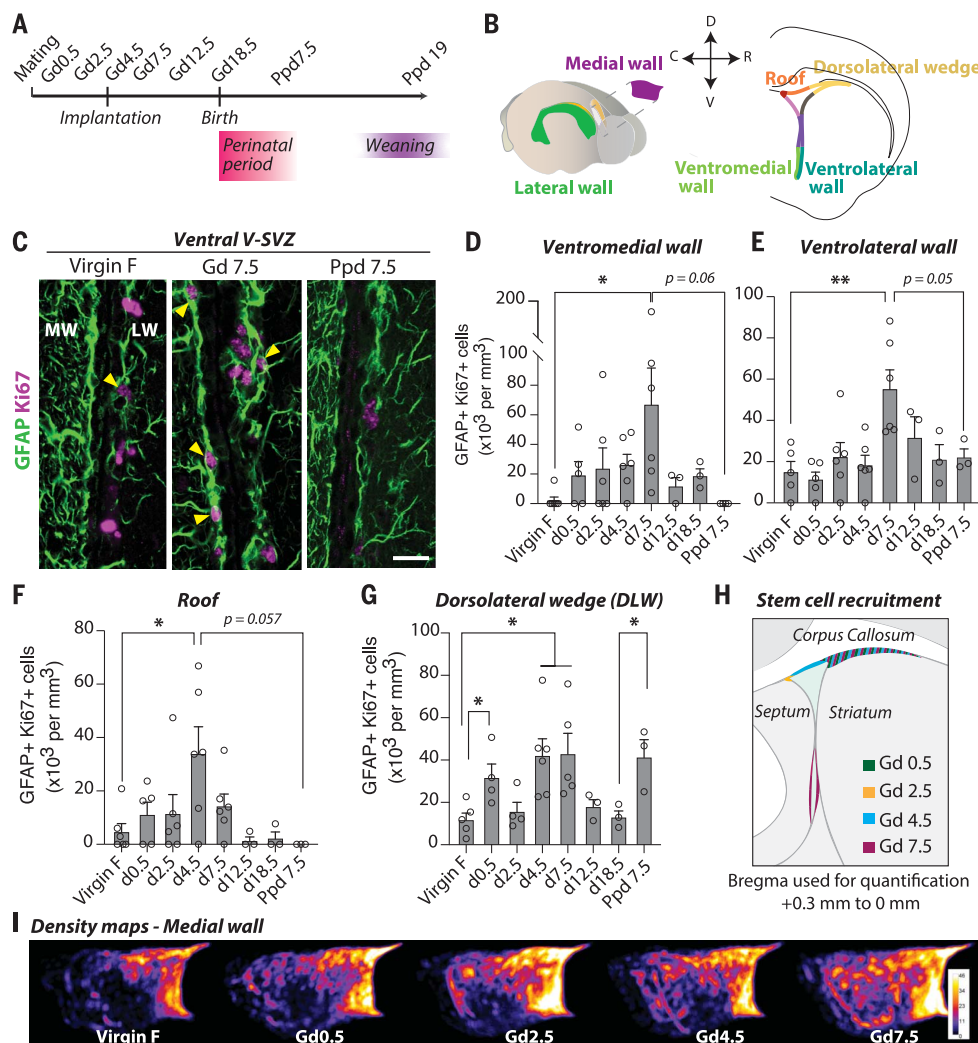


Fig. 1. Dynamic spatial and temporal response of adult V-SVZ NSCs to pregnancy. (A) Overview of the gestation and postpartum periods in mothers. (B) Left: Schema of a mouse brain showing location of the V-SVZ along the lateral wall (green), the medial wall (magenta), and roof of the lateral ventricle (orange). Right: Schema of a coronal section of the V-SVZ highlighting domains analyzed for NSC proliferation. (C) Representative images of dividing NSCs (arrowheads) (GFAP, green and Ki67, magenta) in the ventral V-SVZ. (D to G) Quantification of dividing NSCs in regionally distinct V-SVZ domains. (H) Summary schema of temporal and spatial recruitment of V-SVZ stem cell domains during pregnancy. (I) Averaged MCM2 density maps of the medial wall for each time point ($N = 3$). Scale indicates intensity. Scale bar, 20 μ m. MW, medial wall; LW, lateral wall; C, caudal; R, rostral; D, dorsal; V, ventral.

neurons decreased between 20 and 30 dpi (Fig. 2, G to I, and fig. S5G). Pregnancy-related interneurons in the GCL had been completely culled by weaning (Fig. 2G), but in the MCL (Fig. 2H) and in the AOB (fig. S5G), a few neurons born on Gd 7.5 persisted. These results reveal that pregnancy triggers the addition of transient neurons to distinct layers of the OB, coinciding with birth and the early perinatal period, which disappear by periweaning.

Spatial transcriptomics reveals OB remodeling in motherhood

To gain insight into the molecular correlates of OB remodeling during the perinatal [post-natal day 6 (P6)] and periweaning (P19) periods, we performed Visium spatial transcriptomics (Fig. 3A and fig. S7, A to F). Unbiased clustering of the transcriptomic data resulted in 12 clusters, which predominantly corresponded to anatomical layers, and highlighted sublayer molecular differences such as the superficial and deep GCL in the MOB (Fig. 3B and fig. S7, C and D). Two AOB clusters were present (GCL and MCL/EPL) that were distinct from

MOB, supporting functional differences between these OB structures (21). We validated the expression of markers for each cluster, some of which were highly specific (fig. S7, G and H), using the Allen Brain Atlas in situ database. These data can be explored using a web-based application.

Comparison of the whole MOB and AOB transcriptomes of perinatal mothers to virgin mice (fig. S7A) revealed an up-regulation of Gene Ontology (GO) processes related to synaptic remodeling and the generation of neurons (fig. S8, A and B), which we validated by RNAscope of selected candidate genes (*Elp3*, *Egr1*, *Nr4a3*, and *Klf9*) (fig. S8C). Most up-regulated genes were maintained in mothers through periweaning (table S2) and coded for ribosome biogenesis and translation, mitochondrial function, and neuronal plasticity (Fig. 3C; fig. S8, D to F; and table S2). By contrast, genes that were transiently up-regulated perinatally and subsequently down-regulated between the perinatal and weaning period (Fig. 3C, fig. S8D, and tables S1 and S2) were related to neuronal development and migration, inde-

pendently confirming the transient nature of pregnancy-associated neurogenesis, as well as circadian rhythm and hormonal responses (Fig. 3C and table S2). Pairwise comparison of differentially expressed genes selectively up-regulated perinatally or at periweaning in each cluster (figs. S7A and S9A and table S3) revealed the spatial enrichment of specific biological processes in distinct OB layers (fig. S9, B to D, and table S4), with more extensive remodeling perinatally (fig. S9C) than at periweaning (fig. S9D).

Two clusters (clusters 4 and 9) were enriched in mothers compared with virgins (Fig. 3D and fig. S10, A to C), which was confirmed in a sensitivity analysis (see the materials and methods, fig. S11, and table S5). Cluster 4 sequencing spots were distributed across the outer layers of the OB (superficial GCL/MCL/EPL/GL) (fig. S10A), whereas cluster 9 was localized in both superficial and deep GCL (fig. S10B). Cluster 4 and 9 enriched genes contributed to GO processes related to neurogenesis, gliogenesis, behavior, and blood vessel remodeling (Fig. 4A, fig. S10D, and table

Fig. 2. Pregnancy-associated OB interneuron subtypes are transient. (A) Schema of pulse-chase experiment on different gestation days and physiological phases corresponding to 20 and 30 dpi. (B) Schema of different layers in MOB and AOB. (C to F) Fold change quantification of analog⁺ NeuN⁺ neurons generated on different gestation days in distinct OB layers compared with matched virgin controls. (G and H) Quantification of newly generated neurons born on different gestational days at 20 and 30 dpi in the GCL (G) and MCL (H). (I) Representative images of GCL and MCL analog⁺ NeuN⁺ cells (pulsed at Gd 7.5) in virgin female mice perinatally (20 dpi) and at periweaning (30 dpi).

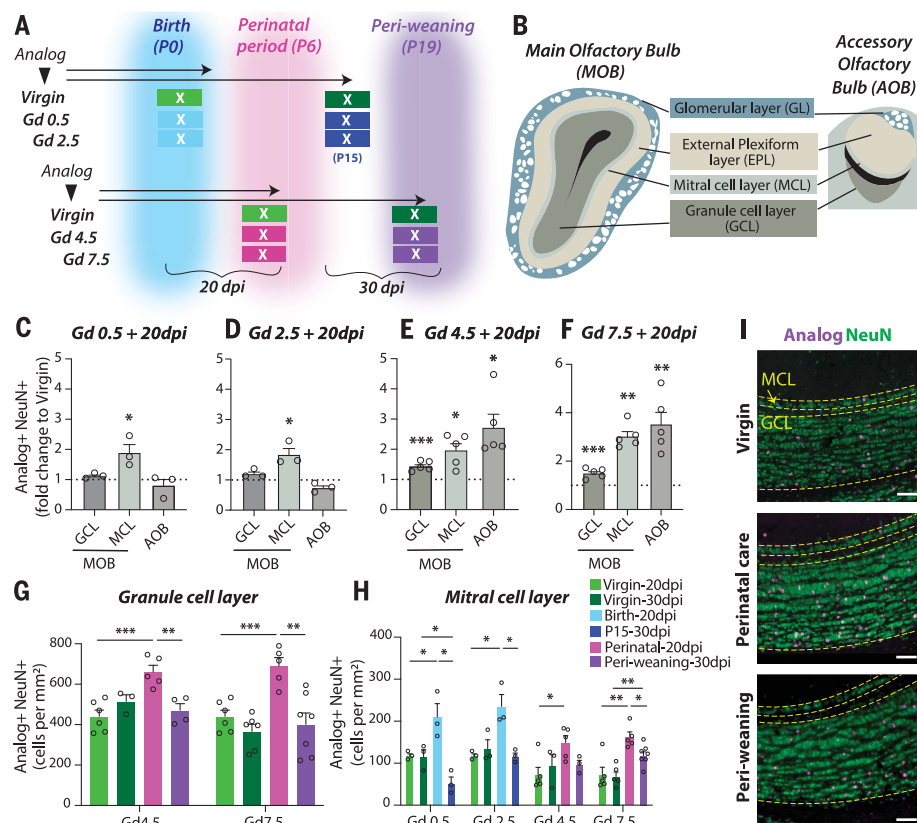
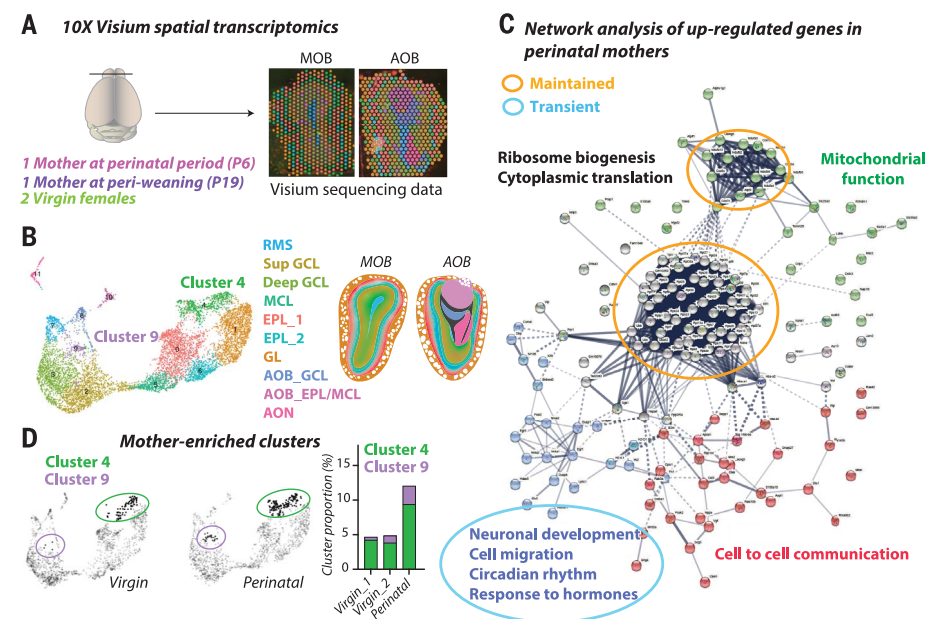


Fig. 3. Spatial transcriptomic analysis of OB remodeling in mothers. (A) 10x Visium spatial transcriptomics of MOB and AOB in virgins and mothers at perinatal care and periweaning. Sequencing spots on sampled OB sections are shown (right). (B) Color-coded schema of anatomical layers in MOB and AOB (right) matching colors in the uniform manifold approximation and projection (UMAP) plot (left). (C) Network analysis of up-regulated genes in perinatal mothers generated using STRING software (<https://string-db.org/>). Orange circles indicate the two regulation hubs maintained through periweaning, and blue circle indicates gene sets transiently up-regulated perinatally. See table S1 for list of genes. (D) Left: UMAP plots from the Shiny app (<https://www.rstudio.com/products/shiny/>) highlighting mother-enriched clusters 4 (green) and 9 (purple) in virgin and perinatal samples. Right: cluster proportions over total number of sequencing spots.



S4). These are therefore ideal clusters with which to identify pregnancy-related interneuron subtypes.

Molecular markers of pregnancy-associated transient OB interneurons

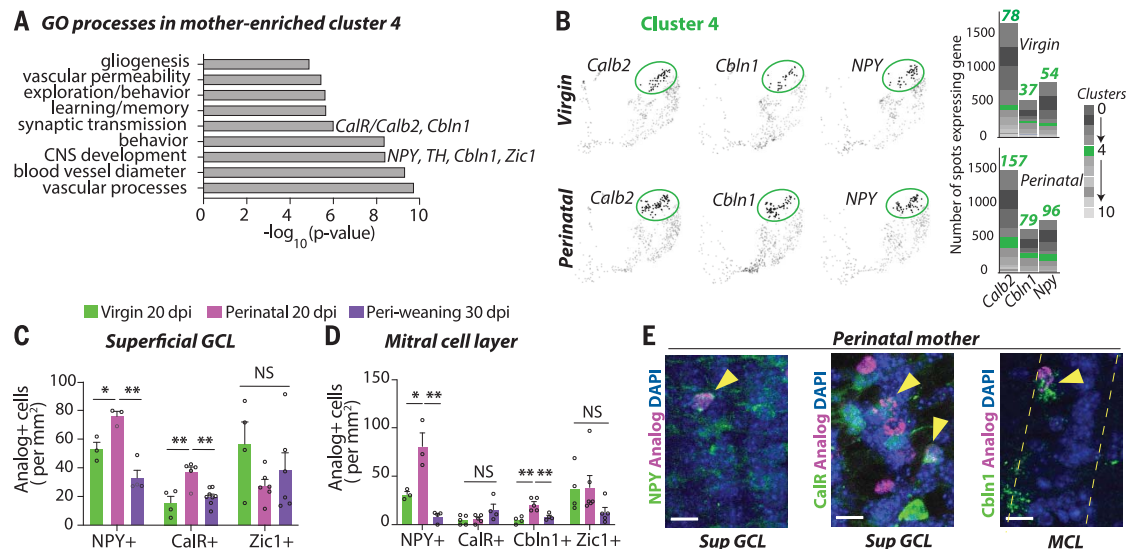
To unravel pregnancy-associated interneuron markers, we focused on mother-enriched clus-

ter 4, because pregnancy-related neurogenesis primarily occurs in the superficial GCL and MCL (figs. S5D and S6, B to D). Both are layers in which adult-generated neurons integrate less under homeostasis and for which few molecular markers are known (15). Enriched genes in cluster 4 included several known interneuron markers, including *NPY*, *Cbln1*, *Calb2*, *Zic1*, and

TH (Fig. 4A), the expression of which is detected in more sequencing spots in perinatal mothers (Fig. 4B). Analog pulse labeling at Gd 4.5 and 7.5 revealed two distinct subpopulations of superficial granule cells that increased during the perinatal period [neuropeptide Y (NPY)⁺ analog⁺ and calretinin (CalR)⁺ analog⁺], whereas *Zic1*⁺ analog⁺ neurons did not change (Fig. 4, C and E,

Fig. 4. Molecular markers of pregnancy-associated interneurons.

(A) GO process analysis for genes enriched in cluster 4 using Metacore (<https://portal.genego.com/>). Selected candidate interneuron markers are shown. **(B)** Left: UMAP plots (from the Shiny app) for interneuron markers displaying their cluster-specific enrichment in mothers perinatally (bottom panels) compared with virgin females (top panels). Right: Quantification of the number of sequencing spots expressing each gene per cluster. Expression is defined as higher than a log-normalized count value of 0.5. **(C and D)** Quantification of analog⁺-colabeled interneurons in superficial GCL (C) and MCL (D). Counts of Gd 4.5 and 7.5 pulsed neurons were pooled. **(E)** Representative pictures of analog⁺ (magenta) NPY, CalR, and Cbln1 cells are shown in green. Yellow arrowheads indicate colabeled cells. Scale bars, 10 μ m.



and fig. S10, E and F). In the MCL, we identified two new adult-generated interneuron subtypes that increased perinatally, NPY⁺ analog⁺ cells in the inner portion and cerebellin1⁺ (Cbln1⁺) analog⁺ cells in the outer portion (Fig. 4, D and E, and fig. S10G). By contrast, analog⁺ cells co-stained with Zic1, CalR, or 5T4 did not change (Fig. 4D and fig. S10H). The increase in pregnancy-related OB interneurons was transient in both the superficial GCL and MCL (Fig. 4, C and D). Cluster 4 also includes sequencing spots located in the GL and tyrosine hydroxylase (TH)⁺, calbindin⁺, and CalR⁺ analog⁺ cells, but not NPY⁺ or Zic1⁺, interneurons increased perinatally (fig. S12, A to F). In contrast to the superficial GCL and MCL, analog⁺ interneurons in the GL were maintained through periweaning (fig. S12A).

Pregnancy-related neurogenesis modulates own pup odor recognition

To investigate the physiological relevance of transient pregnancy-associated interneurons, we assessed their survival dynamics when the perinatal period was prematurely shortened by pup removal at P1 (Fig. 5A) or was extended by cross-fostering until P19 (fig. S13A). Superficial NPY⁺ and CalR⁺ GCL and NPY⁺ and Cbln1⁺ MCL interneurons were all lost at P6 in mothers whose pups were removed at P1 (Fig. 5, B and C). Upon cross-fostering with newborn alien pups every 6 days until the natural time of periweaning, superficial GCL interneurons were maintained (fig. S13, B, D, and E). However, NPY⁺ and Cbln1⁺ MCL interneurons were not (fig. S13, C and D), highlighting the functional heterogeneity of pregnancy-related interneurons. To investigate whether the maintenance of neurons requires

the physical presence of pups, we exposed mothers whose pups were removed at P1 to alien pup nest odor for 6 days (Fig. 5A). This selectively rescued superficial GCL interneurons (Fig. 5B and fig. S13, D and E), but not MCL interneurons (Fig. 5C), in mothers and had no effect on virgin mice (Fig. 5, A and B). Superficial GCL interneurons were not rescued by virgin female nest odor (Fig. 5, A and B), demonstrating that their survival is dependent on pup-related olfactory cues. By contrast, MCL interneurons were lost after own pup removal and were not rescued by either cross-fostering or exposure to alien pup odor, suggesting that their survival may depend on own pup odor.

The dynamic spatial and temporal recruitment of distinct stem cell domains in the V-SVZ makes it challenging to selectively ablate pregnancy-associated neurogenesis. Therefore, to determine the functional relevance of transient neurogenesis during pregnancy, we performed olfactory behavior assays using periweaning mothers and pup removal as models of natural and premature neuronal loss of superficial GCL and MCL interneurons, respectively, and pup odor-rescued mice in which only superficial GCL interneurons were maintained.

To assess whether pregnancy-related MCL interneurons play a role in own pup odor discrimination, we performed habituation-dishabituation olfactory tests using virgin female odor for learning trials and sequential exposure to alien and own pup odor for discrimination trials (Fig. 5D). Virgins did not discriminate alien pup odor, but both perinatal and periweaning mothers did (Fig. 5D). Perinatal mothers could also discriminate own pup from alien odor, but this ability was lost at

periweaning (Fig. 5D). Both pup removal and pup odor-rescued mothers showed altered own and alien pup odor discrimination (Fig. 5D) compared with perinatal mothers, indicating that MCL interneurons play an important role in own pup odor detection, and that maintenance of superficial GCL neurons alone is not sufficient to rescue this. Similar results were obtained when alien and own pup odors were used for habituation-dishabituation (fig. S13F). All mice showed normal pure odor discrimination when exposed to the synthetic odor 1-octanol (Fig. 5E), suggesting that pregnancy-related neurogenesis is involved in pup odor processing rather than global olfactory discrimination.

In a direct comparison of own versus alien P6 pups (fig. S13G), perinatal mothers preferred their own pups compared with mothers after pup removal (fig. S13H). In individual mice, the number of analog⁺ MCL interneurons correlated with own pup visits (fig. S13I). By contrast, the number of analog⁺ superficial GCL interneurons did not (fig. S13J). Therefore, the amount of neurogenesis in the MCL is directly linked to own pup discrimination in mothers.

To investigate the role of pregnancy-related superficial GCL interneurons independently of those in the MCL, we used pup odor-rescued mothers and presented them with P1 alien pups and an inanimate object (fig. S13K). The pup exploration index was decreased in mothers after pup removal and largely recovered in pup odor-rescued mothers, in which superficial GCL interneurons were preserved (fig. S13L). Thus, these neurons enhance preference of pups over other objects and likely modulate stimulus selectivity in perinatal mothers.

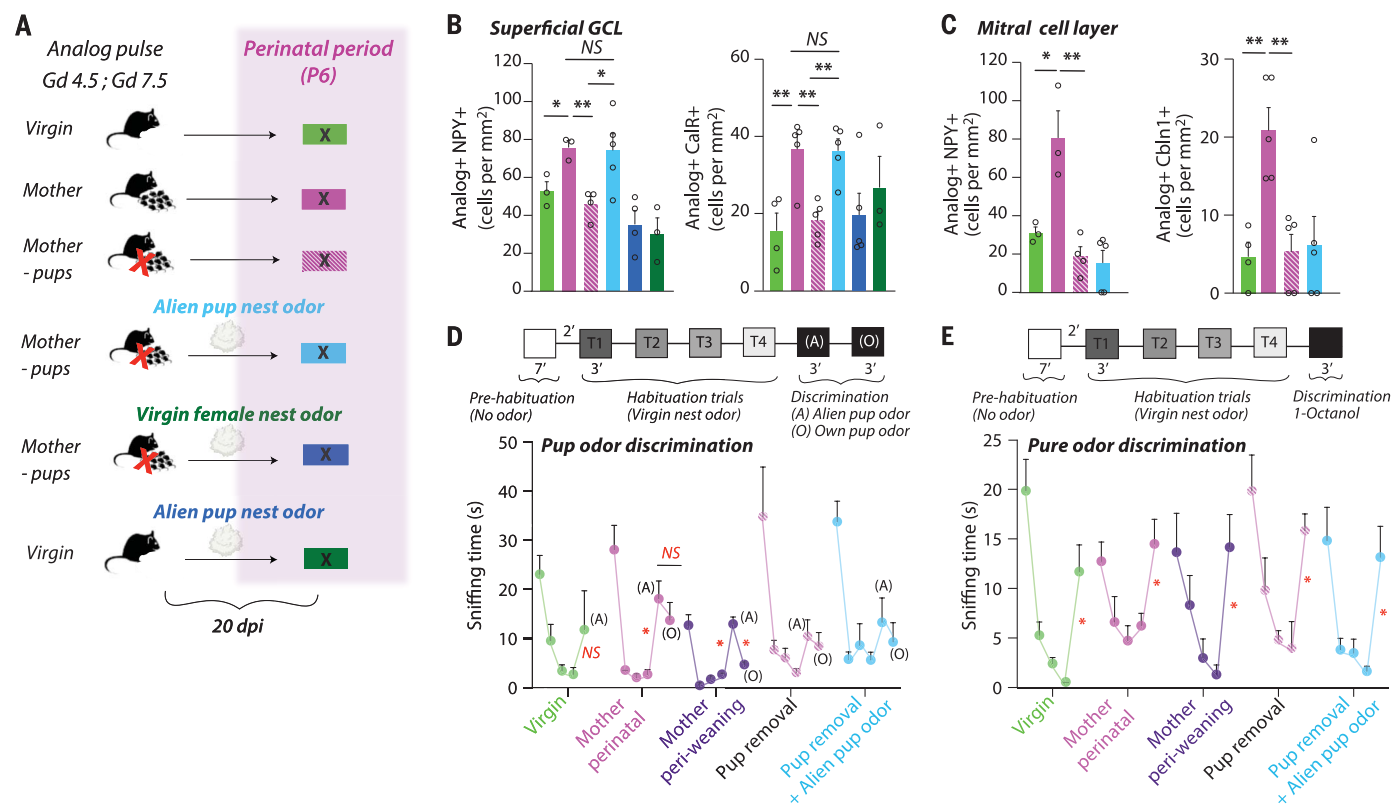


Fig. 5. Physiological relevance of pregnancy-associated transient neurogenesis.

(A) Pup removal and odor exposure experimental design. (B and C) Quantification of effect of pup removal and social odor exposure on Gd 4.5- or Gd 7.5-born pregnancy-associated interneuron subtypes in the superficial GCL (B) and MCL (C). (D and E) Olfactory habituation-dishabituation tests to assess discrimination of

pup odor [(D), “(A),” alien, and then “(O),” own pup odors] and a pure odor [(E), 1-octanol]. Asterisks indicate significant changes between two data points ($P < 0.05$) after ANOVA and post hoc testing with ANOVA. $N = 7$ virgins, $N = 8$ perinatal mothers, $N = 4$ to 6 periweaning mothers, $N = 6$ to 8 mothers after pup removal, and $N = 6$ mothers after pup removal and alien pup odor exposure.

Our findings show that pregnancy-related neurogenesis in the superficial GCL and MCL affects pup odor detection, and that MCL interneurons specifically are key for own pup recognition.

Discussion

Here, we show that the dynamic recruitment of regionally distinct NSCs during early pregnancy for the generation of diverse OB interneurons prepares the maternal brain in anticipation of upcoming physiological needs.

The temporal regulation of spatially distinct adult NSCs in different physiological states is key to understanding the functional relevance of adult neurogenesis. Pregnancy-related interneurons are transient, integrating into layers in which fewer neurons are added under homeostasis, and are important contributors to on-demand OB plasticity. They likely have different intrinsic properties, including higher excitability, than fully mature interneurons (22). This characteristic of pregnancy-related interneurons, together with their ephemeral nature, constitutes a cellular mechanism for adaptive plasticity that is not provided by resident neurons in the OB. Pregnancy-related interneurons may modulate the activity of mitral cells in mothers, making them more sensitive to social

than pure odors (23). Moreover, we show here that own versus alien pup odor discrimination is mediated by transient pregnancy-related interneurons in the MCL, providing a mechanism for familiar offspring odor recognition after parturition described in other mammals such as sheep (24). The number of newly generated neurons in the MCL correlates with own pup preference, raising the exciting possibility that amounts of neurogenesis in individuals can be linked to specific aspects of parental care, perhaps also in males.

The general principle of transient neurogenesis at different time scales in preparation for physiological needs may be conserved across evolution. In songbirds and chickadees, seasonal neurogenesis is linked to seasonal song learning and food caching (25, 26). Our findings reveal shorter time scales over which specific neuronal subtypes are added to OB circuitry for early-life bonding of mothers to their own pup. The culling of these neurons may facilitate the physiological separation from their offspring. In humans, OB neurogenesis largely ends in infancy (27). Our findings suggest that quiescent stem cells may become activated during human pregnancy for transient neurogenesis and underlie the temporary but

substantial changes in the sense of smell experienced by some mothers.

The V-SVZ domain of origin of some interneurons matches stem cell domains that we see recruited during pregnancy (15, 28, 29); however, those generating the pregnancy-related superficial GCL, MCL, and AOB interneurons remain unknown (fig. S13M). Moreover, some recruited stem cell domains are gliogenic (30), raising the possibility that the V-SVZ may also contribute to adaptive oligodendrogenesis and myelination in mothers (31). Future molecular definition of regional stem cell domains will enable more targeted manipulation of NSC pools and neuronal subtypes than the pup removal paradigm that we used here. Our findings further suggest that yet-to-be-identified OB interneuron subtypes are generated in other physiological contexts. It will be important to understand how different physiological states coordinately regulate the generation versus survival of different types of neurons and glia.

Globally, physiological states themselves, including pregnancy, and hunger and satiety (5), regulate spatially distinct NSC pools for on-demand neurogenesis and gliogenesis, decoding the functional relevance of adult NSC heterogeneity.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S13

References (33–39)

Data S1 to S5

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Pregnancy-responsive pools of adult neural stem cells for transient neurogenesis in mothers

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Editor's summary

Different subtypes of new neurons are born in the adult brain ventricular-subventricular zone from spatially distinct pools of neural stem cells (NSCs). However, the physiological relevance of NSC diversity and specificity is unclear. Chaker *et al.* have revealed that during mouse pregnancy, multiple NSC pools are activated in mothers and generate specific olfactory bulb interneurons that function around birth to modulate aspects of maternal care, including own-pup recognition, and then disappear as pups mature (see the Perspective by Kempermann). These results highlight how adult NSC heterogeneity might provide a substrate for adaptive brain plasticity in response to different physiological states. —Mattia Maroso

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