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Commentary

Neural circuit regulation of postnatal and adult subventricular zone neurogenesis: Mechanistic insights, functional models, and circuit-based neurological disorders

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Abstract

Neural circuits' role in regulating neurogenesis within the adult subventricular zone (SVZ) of the lateral ventricles (LV) has been extensively studied over the past two decades. The dynamic interplay between neurons, neurotransmitters, and LV neural stem cells (NSCs) highlights the critical influence of neural circuits on NSC renewal, proliferation, and differentiation. This article explores how neurotransmitters like dopamine, serotonin, GABA, acetylcholine, and glutamate regulate SVZ neurogenesis, revealing the cellular processes essential for NSC modulation and neuroblast generation. Recent studies have identified specific pathways, such as the ACC-subep-ChAT$^+$ circuit, that modulate NSC activity and proliferation through muscarinic receptor activation and intracellular signaling cascades. These findings advance our understanding of the neural circuit basis of NSC regulation, with implications for brain development, neurological disorders, and circuit-based therapeutic strategies. Moreover, the current understanding emphasizes the importance of elucidating neural circuit interactions to fully grasp neurogenesis mechanisms and their relevance to neuronal repair, neurodevelopmental, and neurodegenerative disorders. Addressing the differences between human and rodent neurogenesis could enhance the translation of these insights into improved therapeutic strategies for neurodegenerative conditions. The article also discusses how single-cell multi-omics technologies are transforming the study of these processes, providing new insights into the molecular underpinnings of neurogenesis and neural circuit modulation in health and disease.

Keywords: Subventricular zone, Lateral ventricles, SVZ neurogenesis, ACC-subep-ChAT+ circuit, Brain development, Neurological disorders, Neuronal repair, Circuit-based therapeutic

Mechanisms and Functional Implications of Neural Circuit Regulation of Neurogenesis in the Adult Subventricular Zone

The regulation of postnatal mammalian neurogenesis in the subventricular zone (SVZ) of the lateral ventricles (LV) through neural circuits is of paramount importance. Several Local and distal neurons are crucial in regulating the renewal and differentiation of adult lateral ventricular neural stem cells (LV NSCs), as well as progenitor proliferation and neuroblast generation (**Figure 1**). These neurons influence adult LV NSCs through neurotransmitter signals [1,2]. LV NSCs express a range of receptors, allowing them to respond to these neurotransmitter signals, which are essential for neurogenesis regulation [3]. Neural circuits play a critical role in controlling the cellular mechanisms involved in neurogenesis within the SVZ. Our current understanding raises several questions about the potential regulatory functions of different brain regions in adult neurogenesis through circuit signals.

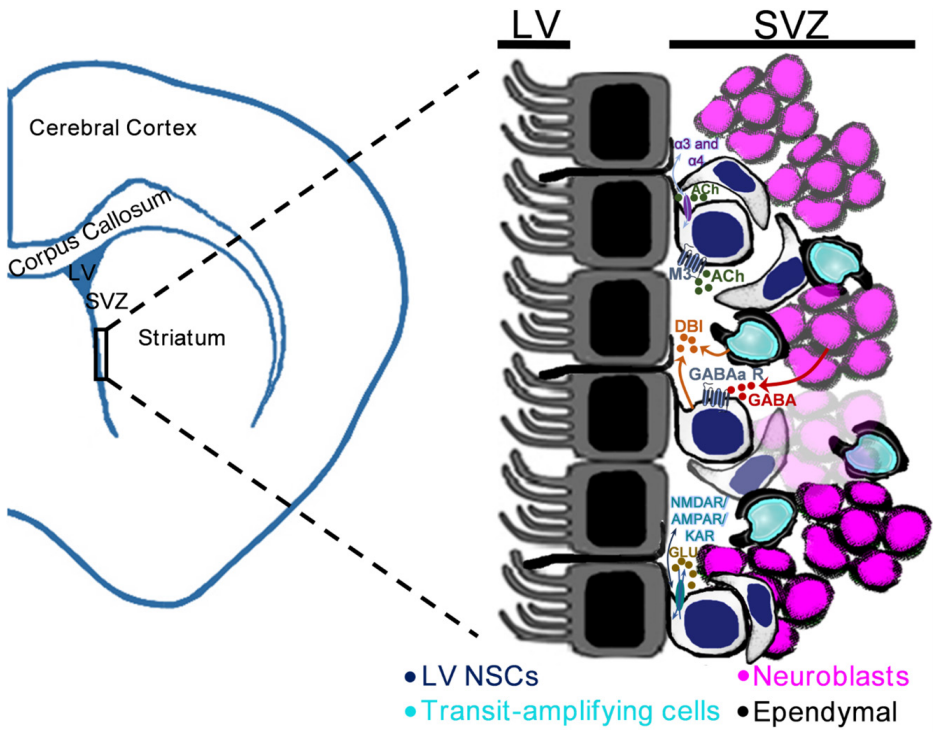

Figure 1. The cellular composition of the SVZ includes ependymal, LV NSCs, TAPs, and neuroblasts, along with neurotransmitters implicated in regulating cellular proliferation and neurogenesis.

Neurogenesis in the postnatal/adult SVZ is a complex process that begins with LV neural stem cells, which can be dormant quiescent NSCs (qNSCs) or actively dividing (aNSCs) [4,5]. These qNSCs activate to self-renew or differentiate into transient amplifying progenitors (TAPs), which become neuroblasts that migrate to the olfactory bulb (OB) and mature into interneurons (**Figures 1 and 2**) [4,6-10].

The neuronal regulation of SVZ neurogenesis has shown various effects. Dopaminergic neurons from the midbrain project to the SVZ niche, and their denervation leads to decreased proliferation of LV NSCs and reduced OB neurogenesis (**Figure 2**) [11]. Additionally, dopamine is crucial for maintaining LV NSCs by inhibiting their division [12]. In contrast, distal serotonergic neurons from the dorsal raphe nucleus (DRN) release serotonin (5-HT) into the SVZ

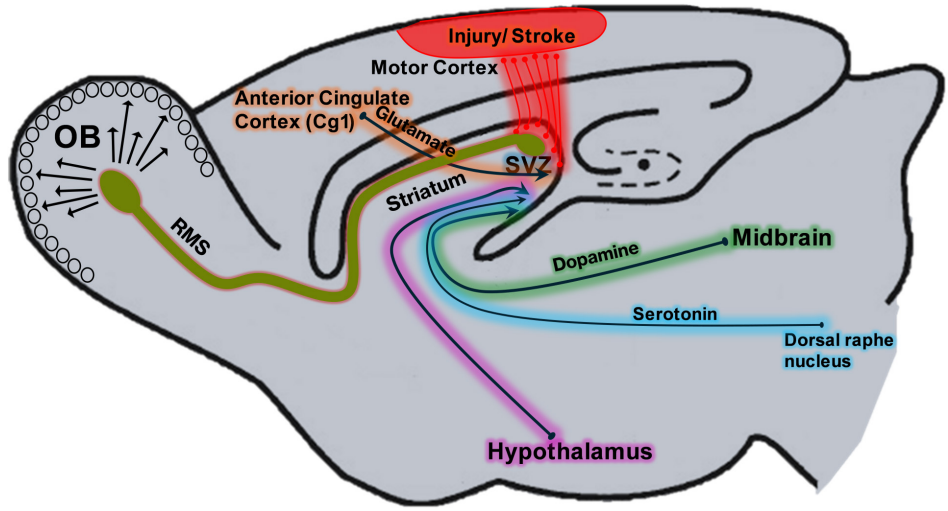

Figure 2. Neural circuits and motor cortex injury/stroke regulate LV NSC proliferation, differentiation, and SVZ neurogenesis.

niche, forming a dense plexus of supraependymal axons that interact with LV NSCs and ependymal cells, thereby promoting LV NSC proliferation and neurogenesis (**Figure 2**) [13-15]. Additionally, proopiomelanocortin (POMC) neurons in the hypothalamus selectively innervate the anterior-ventral SVZ niche, stimulating Nkx2.1+ NSCs to produce distinct OB interneuron subtypes [16] (**Figure 2**).

The neurotransmitter GABA is continuously synthesized and spontaneously released by neuroblasts within the SVZ niche, where it plays a crucial role in controlling LV NSC proliferation and differentiation. It does so by preventing cell-cycle progression and thereby maintaining the NSCs in a quiescent state through activation of GABA_A receptors expressed on these cells [17-20]. GABA-induced depolarization leads to the opening of voltage-gated calcium channels (VGCCs) and subsequent calcium influx, a process that can be effectively blocked by specific antagonists such as nifedipine for L-type channels or mibefradil for T-type channels (**Figure 3**) [21]. Both LV NSCs and TAPs express the diazepam-binding inhibitor protein, which blocks GABAergic receptors and inhibits neurotransmission, thereby promoting cell proliferation [22]. GABA is also involved in SVZ functions, such as enhancing neuroblast maturation [23], and regulating postnatal/adult NSCs by inhibiting their proliferation and differentiation via bulk release into non-synaptic areas [17,22,23].

A small population of cholinergic neurons (subep-ChAT$^+$) in the subependymal space releases acetylcholine (ACh) locally, modulating the proliferation of LV NSCs and neuroblasts in an activity-dependent manner [24]. These subep-ChAT$^+$ neurons receive presynaptic excitatory input from the cingulate cortex area 1 (ACC), which regulates LV NSC proliferation and neurogenesis (**Figure 2**) [25,26].

The activation of acetylcholine receptors (AChRs) induces calcium influx, which subsequently triggers the mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) signaling pathways, thereby regulating cell proliferation and DNA synthesis [27,28]. Intracellular calcium levels can modulate the MAPK cascade through two mechanisms: calcium-dependent tyrosine kinase (PYK2) or calmodulin, both converging on the Ras pathway to activate MAPK (**Figure 3**) [29].

The significant involvement of several specialized neuronal circuits in SVZ neurogenesis should capture attention to understand their molecular components and the signaling pathways involved in regulating cellular symmetrical and asymmetrical division and cellular proliferation, which ultimately participate in regulating the generation of neuroblasts. A recent study revealed a molecular pathway by which cortical circuits (the ACC-subep-ChAT$^+$ circuit) regulate LV qNSCs activation and proliferation through muscarinic receptor 3 (M3) receptors on LV qNSCs (**Figures 2 and 3**). This study demonstrated that the activation of M3 receptors enhances downstream IP3R1 activity on the endoplasmic reticulum, leading to increased intracellular calcium levels. The elevated calcium then activates CAMK2D and MAPK10, resulting in the translocation of pMAPK10 into the nucleus and initiating the proliferation process (**Figure 3**) [30]. This study sheds light on the importance of understanding how neural circuits communicate and modulate NSC activity and control their proliferation through cellular communication across brain regions. Additionally, it highlights the need to investigate the neural regulation of signaling pathways within NSCs and progenitors to better manage their activity based on neural activity under physiological conditions or pathological disorders such as glioblastoma.

Furthermore, LV NSCs have been reported to express muscarinic receptors that respond to acetylcholine, resulting in brief calcium signals through store-operated channels [31,32]. These cells also express ionotropic nicotinic acetylcholine receptors (nAChRs), including the α3 and α4 subtypes (**Figure 3**) [24]. Additionally, α7

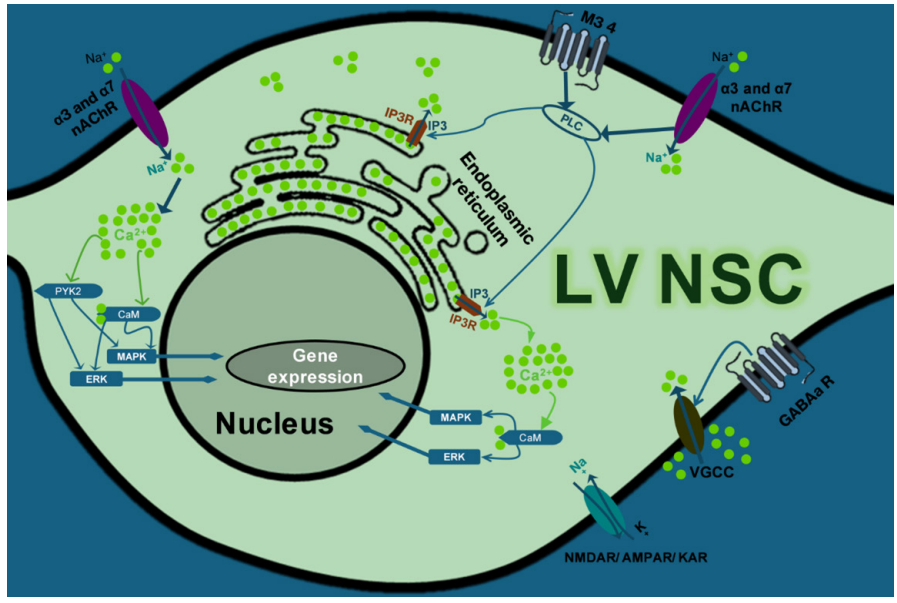

Figure 3. Neurotransmitters expressed on LV NSCs upregulate downstream signaling pathways involved in LV NSC proliferation.

nAChRs are found in the ventricular-subventricular zone (V-SVZ), where they are expressed by neuroblasts and TAPs [33,34]. The activation of local cholinergic neurons or the acute administration of nicotine significantly enhances neurogenesis *in vivo* [24,35]. Pharmacological and genetic studies have shown that α7 nAChRs promote neuronal differentiation while inhibiting the proliferation of V-SVZ cells under normal conditions and in response to ischemia. In contrast, the β2-nAChR subunit plays a crucial role in regulating the survival of newborn neurons [33,36].

Thus, the presence and activity of acetylcholine in the brain, particularly through its interaction with cholinergic receptors and the resulting intracellular calcium influx, serve as critical modulators of neuronal proliferation and differentiation. This underscores acetylcholine's significant role in early brain development and neurogenesis, particularly through the dynamic regulation of calcium signaling pathways.

Beyond GABAergic and cholinergic signaling, NSCs and neuroblasts also express glutamate-responsive ionotropic receptors, including NMDA, AMPA, and kainate subtypes (**Figures 1 and 3**) [20,37]. Although the specific functions of glutamate receptors in NSCs remain under investigation, it is known that kainate and AMPA receptors induce calcium influx in neuroblasts, regulating their migration speed along the lateral ventricles (LV) and promoting proliferation, particularly in the context of brain repair following a stroke [37,38]. Furthermore, glutamate released by astrocytes significantly impacts neuroblast migration and the integration of adult-born neurons into neural circuits [39].

The regulatory mechanisms controlling LV NSCs through neural circuits involve multiple layers of cellular processes, including proliferation, differentiation, and the generation and maturation of neuroblasts. Understanding these processes requires analyzing the intricate interplay between intracellular and intercellular molecular mechanisms that regulate NSC development and physiology. Recent technological advancements, particularly in single-cell and spatial multi-omics technologies, have made it possible to study these processes in unprecedented detail [40].

Single-cell multi-omics technologies enable the comprehensive characterization of cell states and activities by integrating various single-modality omics methods. These methods profile the transcriptome, genome, epigenome, proteome, metabolome, and other emerging omics, providing a holistic view of cellular functions. The integration of these independent yet interrelated datasets has revolutionized molecular cell biology and could potentially offer new insights into NSC regulation through neural circuit modulation.

The impact of single-cell multi-omics technologies is far-reaching, with applications in cell lineage tracing, tumor immunology, cancer genetics, and the mapping of cellular spatial information [41]. The combination of single-cell multi-omics technologies with other techniques, such as electrophysiology, imaging, and neural tracing, holds great potential for advancing our understanding of neural circuit manipulation in LV NSCs.

Deciphering the Neural Circuit Regulation of Neurogenesis in Animal Behavior, Human Development, and Neurological Disorders

The role of distinct neurons in modulating LV NSC proliferation and SVZ neurogenesis enhances the emerging understanding of the interplay between local and distal neural drivers, the biology of LV NSCs, and learning experiences. This suggests a significant connection between circuit-level activity, animal behaviors, and NSC fate decisions—whether to proliferate or differentiate into new neurons. These insights illuminate how animal experiences translate into changes in SVZ niche signaling that impact NSC fate kinetics.

Olfactory bulb neurogenesis in humans has also been reported [42,43]. Solid evidence indicates that active neurogenesis at the lateral ventricular walls continues to generate migratory neuroblasts up to the first two years after birth [44]. However, the reasons for differences between human and rodent neurogenesis remain unclear. Despite this, the analogous process in rodents can help us experimentally understand how early human postnatal brain development is influenced by neural circuitry inputs.

Furthermore, it remains an open question whether neural circuits contribute to human pediatric SVZ neurogenesis and whether these circuits persist during post-pediatric ages in humans. Understanding neuron-glia communication and their functions at adult ages within the neural circuit basis in the SVZ, could potentially elucidate how neural circuits adapt and reorganize throughout human development and aging, potentially revealing novel mechanisms underlying neurodevelopmental and neurodegenerative conditions.

The regulation of adult neurogenesis by neural circuits offers a critical framework for exploring neuronal regeneration in the adult mammalian brain [45,46]. This model is instrumental for investigating how neural circuits modulate neurogenic processes and the underlying mechanisms of neuronal repair. Additionally, the influence of neural circuits on SVZ neurogenesis provides a valuable experimental system for examining how neural stem cells and progenitors respond to neurological disorders and brain injuries [47,48].

Studying the impact of neural circuits on stem cells, progenitors, and neuroblasts can deepen our understanding of their roles in both pediatric neurobiology and across various adult stages (**Figures 1 and 2**). This research is also essential for elucidating the functions of other glial cells, such as astrocytes, in the regulation of neural circuits. Such investigations can lead to a more comprehensive understanding of the dynamic processes that govern neurogenesis and neural circuit function throughout development and in response to injury or disease, including conditions like glioma.

Numerous studies have demonstrated that LV NSCs respond to stroke and cortical injuries by generating new astrocytes, which migrate to the affected areas to facilitate brain repair (**Figure 2**) [48-51]. However, it remains unclear whether stroke influences the modulation of LV NSCs by neural circuits and how this modulation impacts NSC activity. The development of effective stroke therapies has been significantly hampered by our limited understanding of the precise effects of stroke on neural circuits and the subsequent adaptations of these circuits during recovery.

A significant number of stroke survivors are left with lasting disabilities, and beyond rehabilitation therapies such as physical and occupational therapy, few treatment options—like Transcranial magnetic stimulation (TMS) —effectively enhance post-stroke recovery. The recovery process following a stroke is dynamic, with many patients experiencing gradual improvement, particularly in the early stages after the injury.

Recent technological advancements have significantly enhanced our ability to study neural circuits with unmatched temporal and spatial resolution through imaging and single-cell multi-omics technologies. These techniques are increasingly being applied to both animal models of stroke and injury, as well as to human survivors of stroke and injury, providing valuable insights into the molecular, cellular, structural, and functional changes that occur in various neural circuits following a stroke [52]. These advancements also allow for the study of how stroke-induced changes in neural circuits directly regulate LV NSC activity and how these circuits evolve during rehabilitation and therapy. Gaining a deeper understanding of these processes will shed light on the role of circuit regulation in LV NSCs and how these circuits can be harnessed during different stages of recovery—from the early post-stroke period to the later stages of healing.

Circuit-level neuroscientific knowledge has the potential to advance our understanding of psychiatry and therapeutics. It could be applied to translational and preclinical research, enabling the stratification of patients into diagnostic subgroups based on neurobiological phenotypes and the pharmacological enhancement of psychotherapy [53]. Therefore, the sooner circuit-level approaches are embraced, the sooner the field of psychiatry can transition from general behavioral pharmacology to precision medicine. This approach could also be used to explore whether disorders related to the circuit regulation of NSCs can be therapeutically targeted to correct circuit behavior and regulate NSCs.

It has been hypothesized that dysregulations in specific neurocircuits, characterized by changes in the responsivity of certain neuronal populations in specific brain regions, underlie the development and expression of key neurological symptoms [54]. In recent years, multiple studies have examined brain regions involved in the symptomatology of certain neurological disorders in an effort to better understand the underlying mechanisms and develop more effective treatments [55]. Although this approach has not yet been tested in neurological disorders related specifically to the circuit regulation of LV NSCs, it presents a promising avenue for future research. This approach may help determine whether certain neurocircuits are implicated in some disorders and assess their potential as an effective therapeutic option for treating neurological disorders or their related symptoms. Furthermore, incorporating additional components, such as molecular, anatomical, and functional validation, into studies can aid in exploring therapeutic circuit modulation strategies, thereby enhancing our understanding of the development and progression of various circuit-related neurological disorders, with a focus on addressing these disorders at the circuit level.

The regulation of neural circuits governing NSCs in the LV is still an emerging field. Several brain regions potentially involved in the regulation of these NSCs have yet to be identified. A deeper understanding of these circuits could advance our knowledge of diseases related to olfactory functions, including those associated with aging, olfactory learning, and neurogenesis. For example, olfactory impairment is a common symptom in Alzheimer's disease (AD) patients. Changes in brain regions crucial for olfactory processing, such as the olfactory and entorhinal cortices, can emerge early in the disease's progression, often before memory deficits become apparent [56]. However, the potential role of circuits regulating NSCs in contributing to these changes over time has yet to be explored.

Additionally, aging, combined with the accumulation of amyloid β (Aβ), disrupts synaptic connections between granule cells (GCs) and mitral/tufted (M/T) cells in the OB. This disruption leads to increased gamma oscillations, ultimately contributing to olfactory dysfunction [57]. Abnormalities in M/T cells subsequently trigger the release of GABA from GCs and other interneurons, resulting in abnormally heightened low-frequency gamma oscillations within the OB [58]. Since GCs originate from the SVZ and are potentially regulated by neural circuits, the impact of NSC-regulating circuits on GCs could be critical. Studying how aging affects the neural circuit regulation of NSCs may provide insights into the nature of M/T cell interactions with GCs in the OB over time.

Furthermore, impairment of GCs and M/T cells would affect the synaptic plasticity of these cells, leading to dysfunction in olfactory learning and memory [10]. Therefore, understanding the impact of NSC regulation on the neural plasticity of mature and developing GCs in the OB could aid in the early detection of AD. It may also serve as a model system for studying the progression of AD, exploring the possible impact of circuit regulations within the brain, and developing therapeutic strategies for early- and mid-stage AD.

Similar to AD, other neurological disorders that involve changes in or damage to neural circuits, such as depression and multiple sclerosis (MS), require further study to determine whether these disorders are related to or impact the activity of LV NSCs. This research could enhance our understanding of the development of these conditions, identify their primary causes, and lead to better management through improved therapeutic approaches.

Social determinants are important factors that can impact neural circuits [59]. Several studies have characterized both normal populations and those with neuropsychiatric disorders, revealing differences in decision-making and the underlying neuronal circuits associated with these variations [60]. However, no studies have directly examined how social determinants affect the regulation of lateral ventricular (LV) neural stem cell (NSC) activity. Social adaptations are closely linked to our biology, including brain circuitry and function. Mammalian brains have co-evolved with social living [61], enabling us to process and integrate social and environmental information alongside internal physiological cues for decision-making during social interactions. Therefore, sociodemographic factors are crucial for understanding variations in neural circuits among populations exposed to diverse social determinants [62]. The regulation of LV NSCs through neural circuits is likely influenced by these social determinants. Additionally, these adaptations can be altered, as observed in neuropsychiatric disorders. Understanding this relationship can provide insights into how social determinants impact the neural circuit regulation of brain functions and processes, including NSC regulation in both physiological and pathological contexts.

Concluding Remarks

The regulation of neurogenesis in the SVZ through neural circuits represents a dynamic and intricate process that intertwines neurotransmitter signaling, cellular proliferation, and neuronal differentiation. The diverse roles of neurotransmitters such as dopamine, serotonin, GABA, and acetylcholine in modulating the activity of LV NSCs highlight the complexity of neural circuit regulation. These signals influence various stages of neurogenesis, from the quiescence of stem cells to the maturation of new neurons,

underscoring the importance of understanding how these circuits interact and affect neurogenic outcomes. The findings discussed in this article emphasize the need to further elucidate the specific contributions of different neurotransmitter systems and their impact on LV NSC function.

The integration of advanced single-cell and spatial multi-omics technologies could revolutionize our approach to studying the neural circuit regulation of neurogenesis. These tools offer unprecedented insights into the molecular and cellular processes underlying neurogenesis, enabling a more comprehensive understanding of how neural circuits influence stem cell activity and neuronal development. As we advance in our technological capabilities, the ability to precisely map cellular interactions and signaling pathways will provide valuable information for exploring the mechanisms of neurogenic regulation and its implications for brain function and recovery. This knowledge is crucial for developing targeted therapeutic strategies for neurological disorders and improving outcomes for conditions associated with disrupted neurogenesis.

Future research should focus on exploring how neural circuit regulation of LV NSCs is affected by various physiological and pathological states, including aging, stroke, and neurodegenerative diseases such as AD. Understanding the interplay between neural circuits and NSCs in these contexts could reveal novel insights into disease mechanisms and potential therapeutic interventions. Additionally, investigating the impact of social determinants on neural circuit function and NSC regulation could further our understanding of how environmental factors influence brain health and neurogenic processes. By addressing these areas, we can enhance our knowledge of neurogenesis and its regulation, paving the way for innovative approaches to treating neurological conditions and improving overall brain health.

Conflicts of Interest

The authors declare no conflicts of interest.

Availability of Data and Materials

Not applicable.

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Authors' Contributions

M.N. designed and wrote the main manuscript text.

References

1. Jones KS, Connor B. Intrinsic regulation of adult subventricular zone neural progenitor cells and the effect of brain injury. Am J Stem Cells. 2011 Aug 18;1(1):48-58.
2. Obernier K, Alvarez-Buylla A. Neural stem cells: origin, heterogeneity and regulation in the adult mammalian brain. Development. 2019 Feb 18;146(4):dev156059.
3. Berg DA, Belnoue L, Song H, Simon A. Neurotransmitter-mediated control of neurogenesis in the adult vertebrate brain. Development. 2013 Jun;140(12):2548-61.
4. Codega P, Silva-Vargas V, Paul A, Maldonado-Soto AR, Deleo AM, Pastrana E, et al. Prospective identification and purification of quiescent adult neural stem cells from their in vivo niche. Neuron. 2014 May 7;82(3):545-59.
5. Mich JK, Signer RA, Nakada D, Pineda A, Burgess RJ, Vue TY, et al. Prospective identification of functionally distinct stem cells and neurosphere-initiating cells in adult mouse forebrain. Elife. 2014 May 7;3:e02669.
6. Luskin MB. Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. Neuron. 1993 Jul;11(1):173-89.
7. Lois C, Alvarez-Buylla A. Long-distance neuronal migration in the adult mammalian brain. Science. 1994 May 20;264(5162):1145-8.
8. Lois C, García-Verdugo JM, Alvarez-Buylla A. Chain migration of neuronal precursors. Science. 1996 Feb 16;271(5251):978-81.
9. Doetsch F, Caillé I, Lim DA, García-Verdugo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell. 1999 Jun 11;97(6):703-16.
10. Naffaa MM. Neurogenesis dynamics in the olfactory bulb: deciphering circuitry organization, function, and adaptive plasticity. Neural Regen Res. 2025 Jun 1;20(6):1565-1581.
11. Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, et al. Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci. 2004 Jul;7(7):726-35.
12. Kippin TE, Kapur S, van der Kooy D. Dopamine specifically inhibits forebrain neural stem cell proliferation, suggesting a novel effect of antipsychotic drugs. J Neurosci. 2005 Jun 15;25(24):5815-23.
13. Brezun JM, Daszuta A. Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. Neuroscience. 1999;89(4):999-1002.
14. Banasr M, Hery M, Printemps R, Daszuta A. Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology. 2004 Mar;29(3):450-60.
15. Tong CK, Chen J, Cebrián-Silla A, Mirzadeh Z, Obernier K, Guinto CD, et al. Axonal control of the adult neural stem cell niche. Cell Stem Cell. 2014 Apr 3;14(4):500-11.
16. Paul A, Chaker Z, Doetsch F. Hypothalamic regulation of regionally distinct adult neural stem cells and neurogenesis. Science. 2017 Jun 30;356(6345):1383-6.
17. Liu X, Wang Q, Haydar TF, Bordey A. Nonsynaptic GABA signaling in postnatal subventricular zone controls proliferation of GFAP-expressing progenitors. Nat Neurosci. 2005 Sep;8(9):1179-87.
18. Fernando RN, Eleuteri B, Abdelhady S, Nussenzweig A, Andäng M, Ernfors P. Cell cycle restriction by histone H2AX limits proliferation of adult neural stem cells. Proc Natl Acad Sci U S A. 2011 Apr 5;108(14):5837-42.
19. Daynac M, Chicheportiche A, Pineda JR, Gauthier LR, Boussin FD, Mouthon MA. Quiescent neural stem cells exit dormancy upon alteration of GABAAR signaling following radiation damage. Stem Cell Res. 2013 Jul;11(1):516-28.
20. Khatri P, Obernier K, Simeonova IK, Hellwig A, Hölzl-Wenig G, Mandl C, et al. Proliferation and cilia dynamics in neural stem cells prospectively isolated from the SEZ. Sci Rep. 2014 Jan 22;4:3803.
21. Young SZ, Platel JC, Nielsen JV, Jensen NA, Bordey A. GABA(A) Increases Calcium in Subventricular Zone Astrocyte-Like Cells Through L- and T-Type Voltage-Gated Calcium Channels. Front Cell Neurosci. 2010 Apr 8;4:8.
22. Alfonso J, Le Magueresse C, Zuccotti A, Khodosevich K, Monyer H. Diazepam binding inhibitor promotes progenitor proliferation in

the postnatal SVZ by reducing GABA signaling. Cell Stem Cell. 2012 Jan 6;10(1):76-87.

23. Young SZ, Taylor MM, Wu S, Ikeda-Matsuo Y, Kubera C, Bordey A. NKCC1 knockdown decreases neuron production through GABA(A)-regulated neural progenitor proliferation and delays dendrite development. J Neurosci. 2012 Sep 26;32(39):13630-8.
24. Paez-Gonzalez P, Asrican B, Rodriguez E, Kuo CT. Identification of distinct ChAT$^+$ neurons and activity-dependent control of postnatal SVZ neurogenesis. Nat Neurosci. 2014 Jul;17(7):934-42.
25. Naffaa MM, Khan RR, Kuo CT, Yin HH. Cortical regulation of neurogenesis and cell proliferation in the ventral subventricular zone. Cell Rep. 2023 Jul 25;42(7):112783.
26. Naffaa MM. Significance of the anterior cingulate cortex in neurogenesis plasticity: Connections, functions, and disorders across postnatal and adult stages. Bioessays. 2024 Mar;46(3):e2300160.
27. Zhao WQ, Alkon DL, Ma W. c-Src protein tyrosine kinase activity is required for muscarinic receptor-mediated DNA synthesis and neurogenesis via ERK1/2 and c-AMP-responsive element-binding protein signaling in neural precursor cells. J Neurosci Res. 2003 May 1;72(3):334-42.
28. Jiménez E, Montiel M. Activation of MAP kinase by muscarinic cholinergic receptors induces cell proliferation and protein synthesis in human breast cancer cells. J Cell Physiol. 2005 Aug;204(2):678-86.
29. Rosenblum K, Futter M, Jones M, Hulme EC, Bliss TV. ERKI/II regulation by the muscarinic acetylcholine receptors in neurons. J Neurosci. 2000 Feb 1;20(3):977-85.
30. Naffaa MM, Yin HH. A Cholinergic Signaling Pathway underlying Cortical Circuit Regulation of Lateral Ventricle Quiescent Neural Stem Cells. bioRxiv. 2023 Sep 5:2023-09.
31. Somasundaram A, Shum AK, McBride HJ, Kessler JA, Feske S, Miller RJ, et al. Store-operated CRAC channels regulate gene expression and proliferation in neural progenitor cells. J Neurosci. 2014 Jul 2;34(27):9107-23.
32. Domenichini F, Terrié E, Arnault P, Harnois T, Magaud C, Bois P, et al. Store-Operated Calcium Entries Control Neural Stem Cell Self-Renewal in the Adult Brain Subventricular Zone. Stem Cells. 2018 May;36(5):761-74.
33. Narla ST, Klejbor I, Birkaya B, Lee YW, Morys J, Stachowiak EK, et al. Activation of developmental nuclear fibroblast growth factor receptor 1 signaling and neurogenesis in adult brain by α7 nicotinic receptor agonist. Stem Cells Transl Med. 2013 Oct;2(10):776-88.
34. Sharma G. The dominant functional nicotinic receptor in progenitor cells in the rostral migratory stream is the α3β4 subtype. J Neurophysiol. 2013 Feb;109(3):867-72.
35. Mudò G, Belluardo N, Mauro A, Fuxe K. Acute intermittent nicotine treatment induces fibroblast growth factor-2 in the subventricular zone of the adult rat brain and enhances neuronal precursor cell proliferation. Neuroscience. 2007 Mar 16;145(2):470-83.
36. Wang J, Lu Z, Fu X, Zhang D, Yu L, Li N, et al. Alpha-7 Nicotinic Receptor Signaling Pathway Participates in the Neurogenesis Induced by ChAT-Positive Neurons in the Subventricular Zone. Transl Stroke Res. 2017 May 27:10.1007/s12975-017-0541-7.
37. Platel JC, Dave KA, Bordey A. Control of neuroblast production and migration by converging GABA and glutamate signals in the postnatal forebrain. J Physiol. 2008 Aug 15;586(16):3739-43.
38. Song M, Yu SP, Mohamad O, Cao W, Wei ZZ, Gu X, et al. Optogenetic stimulation of glutamatergic neuronal activity in the striatum enhances neurogenesis in the subventricular zone of normal and stroke mice. Neurobiol Dis. 2017 Feb;98:9-24.
39. Platel JC, Dave KA, Gordon V, Lacar B, Rubio ME, Bordey A. NMDA receptors activated by subventricular zone astrocytic glutamate are critical for neuroblast survival prior to entering a synaptic network. Neuron. 2010 Mar 25;65(6):859-72.
40. Vandereyken K, Sifrim A, Thienpont B, Voet T. Methods and applications for single-cell and spatial multi-omics. Nat Rev Genet. 2023 Aug;24(8):494-515.
41. Baysoy A, Bai Z, Satija R, Fan R. The technological landscape and applications of single-cell multi-omics. Nat Rev Mol Cell Biol. 2023 Oct;24(10):695-713.
42. Bédard A, Parent A. Evidence of newly generated neurons in the human olfactory bulb. Brain Res Dev Brain Res. 2004 Jul 19;151(1-2):159-68.
43. Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelso C, et al. Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science. 2007 Mar 2;315(5816):1243-9.
44. Sanai N, Nguyen T, Ihrie RA, Mirzadeh Z, Tsai HH, Wong M, et al. Corridors of migrating neurons in the human brain and their decline during infancy. Nature. 2011 Sep 28;478(7369):382-6.
45. Ihrie RA, Alvarez-Buylla A. Lake-front property: a unique germinal niche by the lateral ventricles of the adult brain. Neuron. 2011 May 26;70(4):674-86.
46. Lazarini F, Lledo PM. Is adult neurogenesis essential for olfaction? Trends Neurosci. 2011 Jan;34(1):20-30.
47. Robel S, Berninger B, Götz M. The stem cell potential of glia: lessons from reactive gliosis. Nat Rev Neurosci. 2011 Feb;12(2):88-104.
48. Benner EJ, Luciano D, Jo R, Abdi K, Paez-Gonzalez P, Sheng H, et al. Protective astrogenesis from the SVZ niche after injury is controlled by Notch modulator Thbs4. Nature. 2013 May 16;497(7449):369-73.
49. Saha B, Peron S, Murray K, Jaber M, Gaillard A. Cortical lesion stimulates adult subventricular zone neural progenitor cell proliferation and migration to the site of injury. Stem Cell Res. 2013 Nov;11(3):965-77.
50. Faiz M, Sachewsky N, Gascón S, Bang KW, Morshead CM, Nagy A. Adult Neural Stem Cells from the Subventricular Zone Give Rise to Reactive Astrocytes in the Cortex after Stroke. Cell Stem Cell. 2015 Nov 5;17(5):624-34.
51. Williamson MR, Le SP, Franzen RL, Donlan NA, Rosow JL, Nicot-Cartsonis MS, et al. Subventricular zone cytogenesis provides trophic support for neural repair in a mouse model of stroke. Nat Commun. 2023 Oct 10;14(1):6341.
52. Campos B, Choi H, DeMarco AT, Seydell-Greenwald A, Hussain SJ, Joy MT, et al. Rethinking Remapping: Circuit Mechanisms of Recovery after Stroke. J Neurosci. 2023 Nov 8;43(45):7489-500.
53. Ford CL, Young LJ. Translational opportunities for circuit-based social neuroscience: advancing 21st century psychiatry. Curr Opin Neurobiol. 2021 Jun;68:1-8.
54. Sheynin J, Liberzon I. Circuit dysregulation and circuit-based treatments in posttraumatic stress disorder. Neurosci Lett. 2017 May 10;649:133-8.
55. Duval ER, Javanbakht A, Liberzon I. Neural circuits in anxiety and stress disorders: a focused review. Ther Clin Risk Manag. 2015 Jan 23;11:115-26.

56. Murphy C. Olfactory and other sensory impairments in Alzheimer disease. Nat Rev Neurol. 2019 Jan;15(1):11-24.

57. Li W, Li S, Shen L, Wang J, Wu X, Li J, et al. Impairment of Dendrodendritic Inhibition in the Olfactory Bulb of APP/PS1 Mice. Front Aging Neurosci. 2019 Jan 24;11:2.

58. Chen M, Chen Y, Huo Q, Wang L, Tan S, Misrani A, et al. Enhancing GABAergic signaling ameliorates aberrant gamma oscillations of olfactory bulb in AD mouse models. Mol Neurodegener. 2021 Mar 4;16(1):14.

59. Ferreira-Fernandes E, Peça J. The Neural Circuit Architecture of Social Hierarchy in Rodents and Primates. Front Cell Neurosci. 2022 May 12;16:874310.

60. Báez-Mendoza R, Vázquez Y, Mastrobattista EP, Williams ZM. Neuronal Circuits for Social Decision-Making and Their Clinical Implications. Front Neurosci. 2021 Oct 1;15:720294.

61. Dunbar RI, Shultz S. Evolution in the social brain. Science. 2007 Sep 7;317(5843):1344-7.

62. Hackman DA, Farah MJ, Meaney MJ. Socioeconomic status and the brain: mechanistic insights from human and animal research. Nat Rev Neurosci. 2010 Sep;11(9):651-9.