Review

Aberrant Hippocampal Neuroregenerative Plasticity in Schizophrenia: Reactive Neuroblastosis as a Possible Pathocellular Mechanism of Hallucination

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Abstract
Hallucination is a sensory perception that occurs in the absence of external stimuli during abnormal neurological disturbances and various mental diseases. Hallucination is recognized as a core psychotic symptom and is particularly more prevalent in individuals with schizophrenia. Strikingly, a significant number of subjects with Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and other neurological diseases like cerebral stroke and epileptic seizure also experience hallucination. While aberrant neurotransmission has been linked to the neuropathogenic events of schizophrenia, the precise cellular mechanism accounting for hallucinations remains obscure. Neurogenesis is a cellular process of producing new neurons from the neural stem cells (NSC)-derived neuroblasts in the brain that contribute to the regulation of pattern separation, mood, olfaction, learning, and memory in adulthood. Impaired neurogenesis in the hippocampus of the adult brain has been linked to stress, anxiety, depression, and dementia. Notably, many neurodegenerative disorders are characterized by the mitotic and functional activation of neuroblasts and cell cycle re-entry of mature neurons leading to a drastic alteration in neurogenic process, known as reactive neuroblastosis. Considering their neurophysiological properties, the abnormal integration of neuroblasts into the existing neural network or withdrawal of their connections can lead to abnormal synaptogenesis, and neurotransmission. Eventually, this would be expected to result in altered perception accounting for hallucination. Thus, this article emphasizes a hypothesis that aberrant neurogenic processes at the level of reactive neuroblastosis could be an underlying mechanism of hallucination in schizophrenia and other neurological diseases.

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Introduction

Background of Schizophrenia

Schizophrenia is a debilitating neuropsychiatric disorder, characterized mainly by persistent hallucination, delusions, social withdrawal, emotional dysregulation, agitation, and cognitive deficits [1–3]. Initially, Emil Kraepelin described the clinical features of this peculiar affective disorder as dementia praecox, and manic depression due to the admixer of behavioral deformities overlapping with various mental illnesses [4]. Later on, the term schizophrenia was suggested by Eugen Bleuler in 1908 and he extended the description for the clinical signature of schizophrenia with the different positive and negative symptoms [2, 5]. While frequent episodes of hallucinations, delusions, paranoia, abnormal exhilaration, irrational thinking, and inexplicable behaviors are the positive symptoms of schizophrenia, the obvious negative symptoms comprise speech disorders, apathy, emotional blunting, and catatonia [6, 7]. The affective symptoms of schizophrenia include anxiety, depression, and suicidal thoughts, while an increased tendency of aggressive symptoms such as violent verbal abuse and assaultive behaviors are associated with schizophrenia [8, 9]. Besides, a considerable degree of memory loss, deterioration of interpersonal skills, and attention deficits are the key cognitive deficits noticed in schizophrenia [4, 10] (Fig 1).

The clinical symptoms of schizophrenia in childhood are rare, and the behavioral pathology typically develops in the late teenage [11, 12]. The prevalence of schizophrenia is almost 1% of the global population regardless of gender and ethnicity [1, 13]. Presently, there are no structured diagnostic strategies and confirmative biomarkers available to delineate the behavioral symptoms and pathogenesis of schizophrenia, because the etiology of the disease is not distinctive, the abnormal behavioral patterns are comorbid, vary among patients, and differ over time. The symptoms of schizophrenia appear to often co-occur with Bipolar disorder, Obsessive-compulsive disorder (OCD), and Major depressive disorder (MDD) [14, 15]. Despite the accumulation of enormous clinical reports and case studies, the precise causative factor and distinguished pathogenic mechanisms accountable for the onset and progression of schizophrenia remain to be established. There has been considerable progress made in the identification of therapeutic targets for schizophrenia with the aid of recent advancements in genome-wide studies, metabolomics, and proteomics approaches in combination with in silco platforms, genetic engineering tools, and stem cell technologies [16–18]. At present, tailored combinations of antipsychotics, antidepressants, and anxiolytic agents are widely used to manage schizophrenia [1, 19]. Though the neuropharmacological approaches, psychotherapy, and cognitive-behavioral interventions are useful in ameliorating the symptoms of schizophrenia, recurrence of clinical episodes has been reported in a significant percentage of patients regardless of the effectiveness of medicines and other types of therapeutic intervention [1, 20]. Considering the facts,
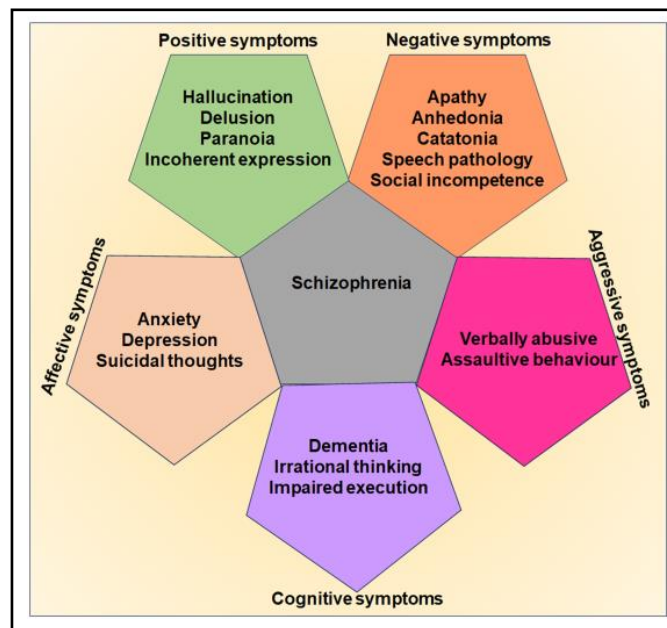

Fig. 1. Clinical symptoms of schizophrenia. The digital representation highlights the key positive, negative, affective, aggressive, and cognitive symptoms of schizophrenia.

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schizophrenia patients require lifelong treatment. Moreover, the available medications appear to subsidize very few specific symptoms and the prolonged treatment has been associated with adverse changes in neurotransmitter levels, and metabolic, and hormonal profiles in schizophrenia patients [19, 21]. Therefore, there is a crucial need for scientific advancement in deciphering the underlying pathogenic determinants of schizophrenia which would help in identifying the ultimate therapeutic target.

Investigations into the underlying mechanisms of schizophrenia have taken many directions, with a particularly promising approach being the study of altered cellular populations in the brain. Focusing on the cellular perspective would provide crucial insights into the pathophysiology of schizophrenia, offering a deeper understanding of the biochemical, molecular, and cellular changes associated with the disorder. Reactive astrogliosis, a pathogenic cellular event associated with an overpopulation of astrocytes, has widely been regarded as a non-neuronal consequence leading to disruption in the electrochemical homeostasis of the brain and creating an imbalance in neurotransmitters during clinical episodes of various brain disorders [22]. Though experimental evidence highlights the alterations in the expression of genes related to astrocytes, the reports on the abnormal astrogliogenic events in schizophrenia are inconsistent [22–25]. Thus, the involvement of astrocytes in the pathogenic events in schizophrenia remains to be further established. Besides, a prominent histopathological signature for the activation of microglial cells, in part responsible for neuroinflammation has also increasingly been evident in the brains of schizophrenic subjects [26, 27]. The prolonged neuroinflammatory response has been known to impair the ongoing neurogenic process and synaptogenesis, collectively impairing the neuroplasticity in the brain [28–31]. Dysregulation of hippocampal neurogenesis is a prominent pathogenic characteristic of various neurodegenerative, mood, and psychiatric disorders including Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), stress, depression, anxiety, and schizophrenia [29, 32–38]. While the progressive decline in hippocampal neurogenesis contributes to the pathomechanisms of various forms of dementia in the aforementioned brain disorders, experimental evidence has established the occurrence of reactive neurogenic processes in the early phases of many neurodegenerative disorders [39–44]. In the physiological state, neuroblasts are considered immature neurons in the developing as well as the adult brain [45, 46]. The neurogenic process involves the proliferation of neural stem cells (NSC), their differentiation into neuroblasts, and the eventual maturation of these neuroblasts into fully functional neurons. The amount of neuroblasts produced in the neurogenic niches determines the degree of neurogenic process in the adult brain which is crucial for neuroregeneration and brain repair [45]. This ongoing neurogenesis plays a key role in the neuroplasticity of the hippocampus, contributing to cognitive functions and mood regulation. Recently, a new line of emerging scientific evidence has identified an abnormal activation profile of neuroblasts, termed reactive neuroblastosis [39, 44, 46–48]. This cellular process involves the overproduction of immature neurons leading to aberrant neurogenesis in the early phase of many neurodegenerative disorders. As neurodegenerative disorders progress into the later stages, the neuroblastosis events appear to be diminished due to the depletion or degeneration of the neuroblasts [44, 46, 47, 49]. Notably, traumatic brain injury, cerebral stroke, and epileptic seizure have also been characterized by reactive neuroblastosis and subsequent abnormal migration of neuroblasts in the affected regions of the brain [48, 50–52]. However, the role of reactive neuroblastosis in the pathogenic process and brain repair remains obscure. Remarkably, recent reports strongly indicate that subjects with AD, PD, HD, and other neurological diseases like cerebral stroke and epileptic seizure experience not only memory loss but also hallucination [53–55]. Considering abnormal neurogenesis as a common factor among both neurodegenerative and psychiatric disorders, the differential modulation of reactive neuroblasts along the disease course could indeed contribute to symptoms like hallucinations and dementia. As the ultimate cell fate of reactive neuroblasts is uncertain, the possibility of their involvement in neuropathogenesis accounting for psychiatric problems and memory functions is very high [44, 49]. The fluctuation in the terminal neurogenic process resulting from reactive

neuroblasts in the adult brain could alter the neuroplasticity responsible for perception, memory, behavior, and consciousness, thereby inducing various psychological stimuli. Therefore, it can be speculated that incidences of hallucination could be correlated with altered neurogenic processes at the level of neuroblast turnover in the brain of subjects with schizophrenia. In the late phase of the disease, depletion of neuroblasts accounting for reduced neurogenesis could be associated with the deterioration of memory function. Therefore, the main aim of the review work is to establish the concept that the differential modulation of reactive neuroblastosis could be an underlying cellular mechanism of hallucination and dementia in schizophrenia. This manuscript has been formulated based on a comprehensive literature search encompassing the clinical, neurophysiological, behavioral, genetic, cellular, and neurogenic aspects of schizophrenia and abnormal neurogenesis processes in other brain disorders that display hallucination and dementia. Various search engines including PubMed were utilized to identify reports on schizophrenia and the regulation of neurogenesis. Highly relevant and recent articles have been considered to prepare the descriptive part, interpretations, and proposed hypothesis in the manuscript.

Risk factors and etiopathological relevance of schizophrenia

The clinical manifestations of schizophrenia are believed to originate from multifactorial elements including some definitive and mostly sporadic gene mutations, copy number variations, epigenetic alterations, dysregulated transcriptomics, chromosomal aberrations, metabolic defects, abnormal brain development, synaptic dysfunctions, impaired neurotransmission, substandard lifestyle and environmental factors [2, 56]. Notably, several key risk factors for schizophrenia have been identified, including maternal malnutrition, preeclampsia, gestational diabetes, prenatal viral infections, vitamin D deficiency, twin gestation, emergency cesarean section, childbirth complications, birth during the winter season, low birth weight, autoimmune diseases, chronic mood disorders, asphyxia, air pollution, illiteracy, and substance abuse, immigration to the foreign country, transcultural influences, living in an urban area and unsuitable environment [2, 57–60]. These diverse factors contribute to the complex interplay of genetic, environmental, and developmental influences implicated in the onset and progression of schizophrenia. Understanding and addressing these risk factors are crucial for effective prevention and management strategies for the disorder. As the mechanisms underlying the pathogenic basis of schizophrenia remain undetermined, the neurodevelopmental hypothesis has widely been considered for the onset and progression of schizophrenia. This hypothesis suggests that disturbances in early brain development, possibly influenced by genetic and environmental factors, predispose individuals to the development of schizophrenia later in life [61, 62]. Understanding the role of early brain development in schizophrenia is crucial for elucidating its etiology and developing more effective therapeutic interventions. During embryogenesis, the generation of neuroblasts from embryonic stem cells (ESCs) is crucial for the development of the brain [63]. The abnormal in-utero condition affecting brain development at the level of neuroblast formation has been considered a prime risk factor for schizophrenia [64, 65]. Therefore, congenital neurogenic defects have been speculated as the underlying cause for the onset of psychotic symptoms and cognitive deficits in the adult stage of life in individuals with schizophrenia [43, 66]. The migration of neuroblasts plays a key role in the morphogenesis of the brain and contributes to the neuroplasticity of the adult brain [67, 68]. Few studies have suggested that the aberrant migration of neuroblasts during early development could be linked with the pathogenesis of schizophrenia in the late stages [65]. A recent study by Jing Yang Tee 2021 indicated that NSCs derived from schizophrenia patients show increased migratory potential than control [69]. Another study by Bon Seong Goo et al. 2023, revealed abnormal neuronal migration in mice and human organoids due to a deficiency in mitotic arrest deficient-1 like (MADL), a schizophrenia-associated gene that regulates the polarity of migrating neurons [70]. Moreover, abnormalities in the disrupted-in-schizophrenia 1

(DISC1) and neuregulin (NRG)-1, the candidate risk genes associated with schizophrenia have been linked to disruption of neuronal migration [65, 71, 72]. The consequences of a reduction or mutation in DISC1 on adult neurogenesis were investigated in experimental mice by Duan et al. Their research found that suppression of DISC1 transcription provoked accelerated dendrite development and migration of neuronal progenitor cells, leading to inappropriate positioning of new neurons in the hippocampus [73]. Therefore, the genetic defects related to neuronal migration in the experimental models of schizophrenia appear to be inconsistent. Moreover, reports on the abnormal migration of neuroblasts in the hippocampus of postmortem brains from individuals with schizophrenia are limited [74]. Thus, the concept linking neuronal migration with the pathogenesis of schizophrenia requires additional scientific confirmation in human studies.

Next, the genes responsible for signal transduction pathways that regulate cell cycle such as iingless-integrated (Wnt), extracellular signal-regulated kinase (ERK), and protein kinase B (PKB) have been reported to be differentially regulated in schizophrenia patients [75, 76]. Further, mRNA levels of cell cycle regulators such as cyclin-dependent kinase (CDK)-4, minichromosome maintenance complex component (MCM)-7, and DNA polymerase delta subunit (POLD)-4 were found to be downregulated in individuals with schizophrenia [77]. Taken together, analysing the gene expression profiles related to the cell cycle and neuronal migration in postmortem brain samples has become crucial for understanding the underlying mechanisms of schizophrenia.

Several other theories have also been postulated for the neuropathogenic basis of schizophrenia. Disruption of glutamate transmission in the thalamocortical areas has been linked to the development of schizophrenia. Various experimental evidence gathered from the use of anesthetic agents namely phencyclidine and ketamine suggest that defects in the expression and function of glutamate decarboxylase (GAD)-1, hypofunction glutamate, and N-methyl-D-aspartate (NMDA) receptors are associated with schizophrenia [78, 79]. While astroglial cells are involved in the neurotransmission of glutamate at the synapses, abnormal astrogenesis during brain development has also been proposed to contribute to the progression of schizophrenia [80]. Further, unusual flux in the release of dopamine and differential expression of its receptors in mesolimbic areas, nigrostriatal, and mesocortical tracts have also strongly been linked to the clinical symptoms of schizophrenia [81]. Increased release and hyper-transmission of dopamine in the subcortical area of the brain are known to contribute to positive symptoms such as hallucinations and delusions in schizophrenia. Convergingly, hypofunction of dopamine resulting from decreased expression or inactivation of dopamine receptors in the prefrontal cortex and caudate nucleus appears to be associated with the development of negative symptoms like anhedonia, lack of motivation, and speech disorders [81, 82]. Experimental studies established from the use of antipsychotic drugs that modulate the serotonergic and dopaminergic systems have revealed that impaired interaction between dopamine and serotonin could prime the abnormal neurochemical events accounting for schizophrenia [83–85]. Furthermore, recent evidence indicates the dysfunctions of GABAergic neurons in the cortex, altered levels of serotonin, and defects in the cholinergic system of the brain during the symptomatic phase of schizophrenia [19, 56, 86, 87]. Additionally, increased levels of norepinephrine have also been suggested to play a role in the pathophysiology of schizophrenia [88].

Considering its heritable nature, many genetic determinants and variants have been linked to the pathogenesis of schizophrenia [89]. First-degree relatives and offspring of individuals with schizophrenia have a considerable chance of manifesting neuropsychological disturbances [57, 89–91]. However, the genetic linkages and the mutations are not unique among schizophrenia patients. The clinical episodes of schizophrenia have been mapped to various polymorphisms or dysregulation of susceptibility genes such as 1) NRG-1, a key factor involved in brain development and vesicular transport of glutamate and epidermal growth factor (EGF) signaling, 2) dystrobrevin-binding protein (DTNBP)-1 which aids in glutamate release, 3) catecholamine O-methyl transferase (COMT), important for signal transduction of dopamine, 4) dopamine beta-hydroxylase (DBH) that catalyzes the

hydroxylation of dopamine and some phenylethylamine derivatives, 5) regulator of g-protein signaling (RGS)-9, responsible for various molecular pathways transduction in the brain and 6) DISC-1, involved in downstream dopamine signaling pathway [92–97]. Eventually, the suicidal behaviors in schizophrenia have been attributed to defects in genes such as the corticotropin-releasing hormone receptor (CRHR)-1 and corticotropin-releasing hormone binding protein (CRHBP), which encode stress response elements involved in the regulation of the hypothalamic-pituitary-adrenal (HPA)-axis [98]. Notably, the aforementioned neurobiochemical and genetic determinants and risk factors appear to be associated with morphological differences and neuroanatomical abnormalities in schizophrenia.

Neuromorphological and pathological alterations in schizophrenia

Owing to its obvious abnormalities in neurotransmission, there has been overwhelming data available for the description of the behavioral deformities and psychotic symptoms in schizophrenia [99]. However, the distinct neuropathological changes of schizophrenia arising from various idiopathic factors have long been refractory to the diagnosis and confirmative tests. Earlier attempts using radiology-based pneumoencephalography unveiled dilated lateral and third ventricles in the brains of subjects with schizophrenia [100, 101]. Subsequently, Johnstone et al. confirmed the presence of enlarged ventricles in schizophrenia patients using axial brain scans [102]. Considerable scientific and technological advancements in recent decades have enabled the implementation of neuroimaging techniques, and neuromorphometric assessments to differentiate the cytoarchitectural alteration and identify the functional defects in the brains of subjects with schizophrenia and those at risk of developing symptoms. In the quest to elucidate the neuropathological changes in the brain, compelling neuroimaging evidence obtained from various medical scanning modalities including computed tomography (CT), magnetic resonance imaging (MRI) with diffusion-tensor imaging (DTI) tractography, magnetic resonance spectroscopy (MRS), magnetoencephalography (MEG) and positron emission tomography (PET)-based studies have collectively demonstrated and validated enlarged ventricles, grey matter loss, structural deformities and structural loss in the corpus callosum, increased volume in basal ganglia, loss of myelination and dysconnectivity of neural network, differences in neurite curvature in schizophrenia [101, 103–105].

To note, the enlarged ventricle has been established as a prominent neuropathological hallmark related to tissue remodelling processes in many neurocognitive diseases as the neuroblasts migrate from the subventricular zone (SVZ) to the pathogenic and degenerating brain sites [106, 107]. Initially, the increased volume of cerebrospinal fluid (CSF) has been proposed for the enlarged ventricles in schizophrenia [108]. The shrinkages in the cortical, striatal, and thalamic areas have been reported to result in ventricular enlargement in schizophrenia [109]. As the evidence for the occurrence of neurodegeneration in schizophrenia is highly limited, reduced grey area has been linked to a combination of neurodevelopmental, genetic, and environmental factors. Notably, reduced neurogenic processes and impaired migration of neuroblasts during the developmental stage have been proposed to contribute to the reduced grey area in the adult stage [65]. According to the neuropil hypothesis, drastic reductions in neural circuity, spine density, and dendritic volume are accountable for grey matter loss in schizophrenia [110]. The histopathological analysis of the postmortem brain samples from individuals with schizophrenia has revealed synaptic loss, rather than neurodegeneration can be responsible for the volume loss in many brain regions [111]. In line with the neurodegenerative hypothesis, few reports indicate the possibilities of pathological neuronal apoptosis and oxidative damage in schizophrenia. However, the role and rationality for the occurrence of apoptotic events in schizophrenia remain ambiguous. Recently, the cell cycle reactivation in mature neurons induced by neuroinflammatory cytokines has been reported to result in reactive neuroblastosis. The cell cycle re-entry of mature neurons would result in synaptic pruning or cell death, thereby

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contributing to reduced grey area in schizophrenia. As proof, some earlier studies highlighted the increased neuronal density in the key brain areas of schizophrenia patients [110, 112]. Eventually, demyelination resulting from the degeneration of oligodendrocytes has been predicted to be the reason for white matter lesions in the frontal cortex, hippocampus, and cerebellum in schizophrenia [84, 113]. A surface-based MRI analysis by Sprooten et al., 2013 intended the widespread cortical thinning, more predominantly in superior frontal, medial parietal, and lateral occipital regions during the early stages of schizophrenia [114]. Therefore, reports on reduced grey matter in schizophrenia require to be revisited and validated with functional neuroimaging and histopathological assessments.

Besides, an analytical study done by Sheffield et al., 2017 using resting-state functional magnetic resonance imaging (rs-fcMRI) revealed that the cognitive impairment noticed in schizophrenic individuals is associated with loss of functional connectivity within and between fronto-parietal lobe and cingulo-opercular networks [115]. Additionally, magnetic resonance spectroscopy and PET-based studies on the brains of schizophrenia patients reported that excitatory-inhibitory imbalance in the cerebello-thalamo-cortical and striato-thalamo-cortical loops, hyperfunction in the mesolimbic dopamine pathway and variations in dopaminergic content in the prefrontal cortex (PFC), anterior cingulate gyrus, and hippocampus contributes to the pathophysiological changes related to development of psychotic disorders in schizophrenia [116, 117] (Fig 2).

A series of MRI-based reports on gross brain morphometric and gyrification assessments unveiled obvious volumetric reduction in the frontal and temporal lobes of schizophrenia subjects [76]. Concomitantly, decreased density of cortical regions and shrinkage in the amygdala, thalamus, nucleus accumbens, and hippocampus have been established as region-specific morphological defects in schizophrenia [120, 121]. Notably, the brains of subjects with schizophrenia have been characterized by reduced hippocampal volume [122]. The reduced hippocampal volume in schizophrenia has been attributed to several factors, including the reduced density of pyramidal cells in the cornu ammonis (CA) regions and decreased neuropil in the molecular layer and hilar region [123]. Similar to the reduced somal sizes noticed in pyramidal neurons of cortical areas, the decreased hippocampal volume
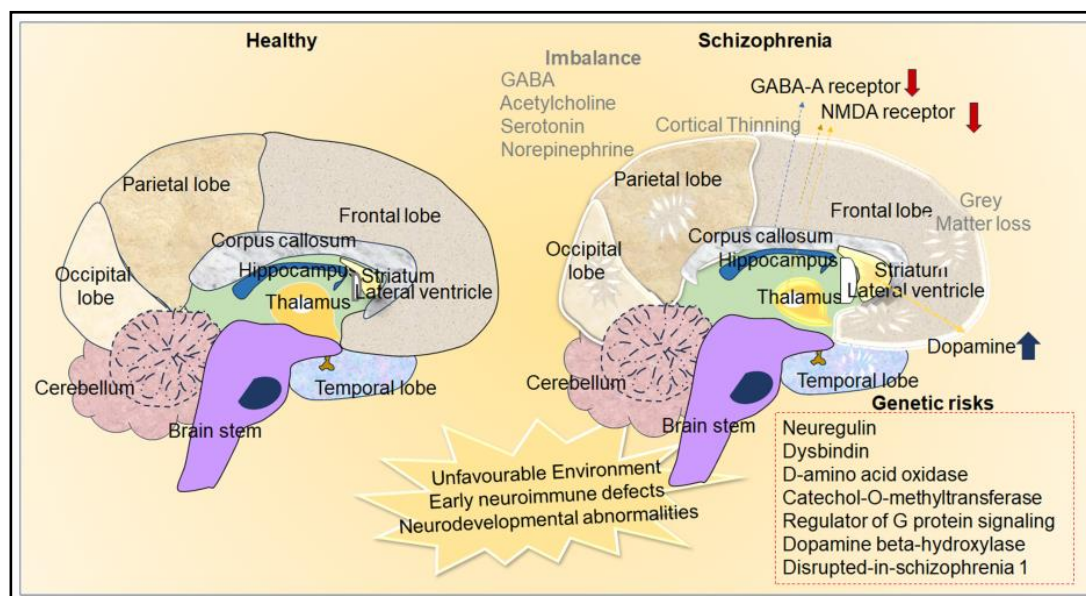

Fig. 2. Neurochemical and anatomical differences in the brain of healthy and schizophrenia. The image depicts the environmental impact, variations in neurotransmission, and hereditary factors as the etiological causes of schizophrenia. Neuroanatomical alterations such as cortical thinning and loss of grey matter in the schizophrenic brain compared to healthy brains.

observed in schizophrenia could be related to decreased somal sizes of pyramidal neurons in CA regions [124]. While some studies have reported reduced overall hippocampal density, few reports have indicated deformity in subareas such as CA1 contributing to the volume loss of the hippocampus [125]. In general, neuronal loss has been considered a primary reason for hippocampal atrophy in many brain and mental disorders [126, 127]. Schizophrenia patients with low serum levels of brain-derived neurotrophic factor (BDNF) and expression of its genetic variant BDNFMet have been characterized by a reduced hippocampal volume [128–130]. Defects in the BDNF signaling pathway have been proposed to result in neuronal shrinkage, and dendritic retraction in the diseased brain which might also contribute to the volume reduction in the hippocampus in many neurodegenerative disorders [131]. While few available postmortem studies of patients with schizophrenia revealed intensified BDNF signaling in the hippocampus, decreased levels of BDNF concentrations in the brain of schizophrenia were also evident [132–134]. However, subsequent studies revealed that there is no association between BDNF and hippocampus volume, therefore, the role of altered BDNF signaling on the hippocampal volume in schizophrenia requires additional investigation.

The extracellular matrix (ECM) contributes to a significant percentage of brain volume [135]. Studies related to abnormalities in reticular structure revealed marked differences in ECM components in the brains of subjects with schizophrenia [136]. Notably, the reduction of the perineuronal nets (PNNs), a key component of ECM that wraps around neurons, axons, and dendrites, gained scientific attention in schizophrenia research [137]. Reduced levels of PNNs have been correlated with structural disorganization and functional loss of key brain areas that are associated with motor sensory and cognitive functions [137, 138]. Thus, abnormalities in PNNs could also be a potential cause of hippocampal volume loss in schizophrenia regardless of neurodegeneration. In the meantime neurogenesis has been considered to play a role in structural and functional aspects of the hippocampus [97]. Therefore, the pathogenic role of ECM disintegration in association with abnormal hippocampal regenerative plasticity in schizophrenia could be an important aspect of scientific consideration.

Among various brain regions, the hippocampus has been considered to play a crucial role in neurocognitive functions as it holds a niche for NSCs [139, 140]. Atrophy or dysfunction of the hippocampus has been linked to dementia, mood, and psychotic disorders [29, 44, 46, 47, 139, 140]. Notably, schizophrenia has been characterized by neuroanatomical, cytoarchitectural, synaptic dissociation, demyelination, microglial activation, and functional abnormalities in association with neuroinflammation in the hippocampus [141, 142]. Distinctly, the ongoing neurogenesis mediated by NSCs-derived neuroblasts has been reported to play a key role in regenerative plasticity, memory, and mood functions [140]. In contrast, defects in the hippocampal neurogenic process have been linked to dementia, stress, anxiety, and depression-related symptoms in various neurological illnesses and traumatic brain injuries [29, 44, 47, 51, 52, 106, 123, 141]. Eventually, abnormal neurogenesis at the level of neuroblast turnover appears to be associated with neurodevelopmental disorders like autism [143]. Therefore, the possibilities for the involvement of aberrant neurogenesis in the hippocampus in the establishment of psychotic disorders cannot be excluded.

While the aging-related progressive cognitive decline has been correlated with a steady decline in hippocampal neurogenesis, recent evidence suggests varying degrees of neurogenesis upon the pathogenic progression in various forms of mental deterioration and neurodegenerative illnesses [144]. Notably, experimental models of schizophrenia have been characterized by arrest in the maturation of the hippocampus due to elevated levels of cellular and molecular signatures of immature neurons [145, 146]. As differential regulation, prolonged dysregulation, and impaired neurogenesis contribute to cognitive deficits, altered neural information processing generated by neurogenic processes in the brain might be associated with hallucinations and memory loss in schizophrenia. Thus, insight into mechanisms that overlap impaired neuroblastosis with hallucinations and dementia could provide advancement in understating the neurobiology of schizophrenia at the level

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of adult neurogenesis. However, the experimental evidence for the involvement of altered neurogenic processes with hallucination is highly limited in human situations. Indeed, many invitro and transgenic animal models of schizophrenia and the outcome of treatment with psychedelic drugs strongly point towards the possibilities for the potential link between altered neurogenesis and hallucination [117, 147–149]. Concurrently, individuals with various neurological diseases who experience hallucination have been found to exhibit abnormal adult neurogenesis [150, 151]. Therefore, the insight into the possible role of adult neurogenesis in the development of hallucination would offer complementary approaches to distinguish the shared pathocellular mechanisms among schizophrenia and other brain diseases.

Reactive neuroblastosis as an underlying mechanism of hallucination in schizophrenia and other neurological diseases

Hallucination is the involuntary emergence of illusory, perceptual, and mystical experiences of the brain that occur devoid of external stimuli through the sensory organs and environment [152]. Hallucination can occur at the level of auditory, visual, tactile, olfactory, and gustatory modalities during conscious as well as in paradoxical sleeping states. Functional neuroimaging studies suggest that the generation of abrupted neural impulses in the key brain areas including the sensory cortex, insula, putamen, and hippocampus could be an underlying cause of hallucination [153–155]. However, the origin of the spontaneous neural activity in the brain that synthesizes substrate for the generation of hallucination remains obscure. Thus far, numerous theories have been proposed for the underlying basis of hallucination [156, 157]. For example, Lopez Ibor proposed that abnormal activation of engram, a hypothetical form of substratum essential for the cognitive process in ideational centers of the brain, can be an underlying basis of hallucination [156, 158]. According to Hughlings Jackson, higher motor centers of the brain are pivotal for intellectual functioning when they are activated spontaneously or independently of peripheral stimuli. Conversely, the deactivation of upper motor centers can elicit the activation of mid-level motor centers, potentially resulting in episodes of hallucination [159, 160]. As per Wilder Penfield's experimental findings, electrical stimulation in certain cortical or subcortical structures could induce different forms of hallucinations [161, 162]. Notably, the occurrence of hallucination is intricately linked to changes in neuroplasticity, particularly within key brain regions such as primary and secondary sensory cortices, basal ganglia, and limbic system including the hippocampus [163]. Among different neurotransmitter-based hypotheses, varying levels of dopamine in the limbic system have been strongly implicated in the development of hallucinations [164]. Emerging research evidence has also highlighted the involvement of other factors such as abnormal immune activation, increased cerebral blood flow, circulating metabolites, and energy metabolism in the brain in the manifestation of hallucinations [165–168]. However, most of the theories that explain hallucinations appear to be merely paradoxical and none have conclusively delineated the definite underlying mechanism of hallucination. Therefore, the pursuit of understanding the root cause of hallucination from various perspectives including at the cellular level has become increasingly important.

Though hallucination is a prominent psychotic symptom of schizophrenia, it also occurs in many other diseases and arises in response to some substance abuse [164]. Indeed, hallucination is a key clinical problem in diverged medical conditions including psychiatric complications and neurodegenerative diseases [169]. Various forms of dementia, bipolar disorder, OCD, epilepsy, cerebral stroke, migraine, brain trauma, brain lesions, brain tumors, metabolic disorders, and Charles bonnet syndrome have been known to be associated with a considerable degree of incidence with hallucination [170]. In addition, individuals with anxiety, stress, depression, and post-traumatic stress disorder (PTSD) have also been known to experience hallucination [171]. In AD, reduced acetylcholinesterase (AChE) activity in the brain has been predicted as a biochemical cause of hallucinations in a significant percentage

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of subjects with progressive memory loss [172, 173]. Eventually, PD and HD patients have also been reported to experience hallucinations which are attributed to imbalances in dopamine and GABA in the limbic system of the brain [55, 174]. However, the occurrence of hallucinations in neurodegenerative disorders is a subject of debate as many drugs that are used for the management therapy of neurological deficits, psychotic problems, sleeping abnormalities, and mood disorders have also been known to induce hallucinations [175]. While there are documented cases of hallucinations associated with prolonged intake of medications like antiepileptic drugs, antidepressants, anticancer medications, and sleeping pills such as narcotics, steroids, pentoxifylline, tramadol, bromocriptine, sertraline, and trazodone, it's important to note that these drugs also exhibit a notable impact on the regulation of hippocampal neurogenesis [176, 177]. Therefore, understanding a specific neuropathogenic signature of schizophrenia that overlaps with other neurological diseases and the mode of action of hallucinogenic drugs and their impact on the regulation of neurogenesis could provide a valid clue in understanding the underlying basis of the hallucinations.

During embryogenesis, the generation of neurons from embryonic NSCs-derived neuroblasts plays a key role in neurodevelopment, whereas defects in the early neurogenic process have been implicated in the pathogenic mechanisms underlying neurodevelopmental disorders and mental disturbances [178, 179]. Among various predictions, a potential link between schizophrenia and aberrant neurogenic events responsible for abnormal brain development in early life has been widely considered to have a negative impact in the latter adulthood stage leading to psychiatric disturbance and neurocognitive impairments [43, 180, 181]. Thus, there has been considerable scientific interest in exploring the alteration of neurogenesis in schizophrenia [182]. In the healthy brain, the degree of neuroblasts generation, accounting for the neuroregenerative characteristics has been directly correlated with mental health, intellectual ability, sexual drive, pattern separation, perception, and cognitive functions, including learning and memory [139, 183–185]. While impaired neurogenesis during fetal development has been linked to intellectual disability disorders, the progressive decline in the neuroblast population followed by the loss of new neurons in the hippocampus has been established as brain aging and distinct neuropathogenic event along with progressive memory loss [47, 139, 144, 184–187]. However, the role of aberrant neurogenesis in pathogenic mechanisms in neuropsychiatric and neurodegenerative disorders has been less explored.

Notably, neurological diseases like epilepsy and cerebral stroke are associated with increased neurogenesis in the hippocampus, unusual migration of neuroblasts in the cortex and striatum, and altered cell fate events in the neurogenic and non-neurogenic areas [48, 51]. A significant percentage of subjects with epileptic seizures and cerebral ischemia have been reported to experience hallucination [188–190]. Besides, physical exercise in a physiological state has been known to enhance cognitive ability by increasing the neurogenesis in the hippocampus [191]. However, aggressive physical exercise appears to exacerbate the disease progression in some neurodegenerative diseases and some individuals experience hallucination after vigorous physical activities [192]. Interestingly, increased level of neuroblast proliferation and their ectopic migration have also become evident in the early phase of neurodegenerative disorders, while the late phase of these disorders with the prominent sign of dementia and depression-related disease have been characterized by diminished levels of neuroblasts in the brain [29, 46, 47, 49, 143, 193]. The ongoing turnover of neuroblasts has generally been confined to the hippocampus and SVZ-OB system, but several reports indicate the possibility for the occurrence and migration of neuroblasts in the other brain regions including the cortex, striatum, and hypothalamus [46, 49, 194–196]. As the astrocytes with radial glial morphology have been identified as the precursors of neuroblasts in the normal brain, the presence of astroglial cells in the non-neurogenic areas has been regarded as an alternate source of NSCs that can give rise to neuroblasts in different areas of the brain during the disease course [197]. Recently, the sustaining of non-newly generated terminally undifferentiated functional neuroblasts has also been reported in the

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brains of some mammals such as dolphins and sheep [198, 199]. These quiescent neuroblasts are likely to be activated upon environmental stimuli or during disease progression [29, 200]. In disease conditions, the abnormal discharge of proinflammatory cytokine from activated immune cells leads to a cell cycle arrest in NSCs which can cause the stimulation of neuroblast proliferation as a compensatory cellular effect [29, 47]. The concept of reactive neuroblastosis has recently been introduced to describe the increased number of neuroblasts in response to neuropathogenic changes in HD. It describes an abnormal cellular condition of the brain in which neuroblasts undergo extensive proliferation and ectopic migration in the non-canonical neurogenic areas [44, 46]. As the concept is evolving presently, the evidence for the occurrence of reactive neuroblastosis can be correlated with the amount of newly originating neurons/neuroblasts that are positive for markers such as DCX, polysialylated neuronal cell adhesion molecule (PSA-NCAM), neurogenic differentiation (NeuroD), NRG-1, and Calretinin in the brain during the disease conditions [201].

Notably, postmortem studies have identified reduced cell proliferation due to low numbers of kiel (Ki)-67 and proliferating cell nuclear antigen (PCNA) immunopositive cells in the hippocampus of schizophrenia victims [202]. Feng et al. indicated that there is no change in mRNA expression of neuroblast markers in schizophrenic brains compared to age-matched controls indicating a compensatory cellular mechanism upon the aging process accounting for enhanced interstitial white matter neurons [203]. Zhang et al. 2002 unveiled no significant differences in the density of calretinin-positive cells in the mid-dentate gyrus implying that reduced NSC proliferation could be compensated by increased neuroblast in the brain of schizophrenia subjects [204, 205]. However, the reduction in the overall cell proliferation did not reflect the number of neuroblasts in the neurogenic area of the brain, as D Barbeau et al., reported that reduction in the number of PSA-NCAM-immunoreactive neuroblasts was confined in the hilar region but not in the hippocampal dentate gyrus (DG) of brains of schizophrenic subjects [206, 207]. These findings suggest a dynamic balance between NSC proliferation and neuroblast production in the pathophysiology of schizophrenia. Interestingly, a recent report from Joen-Rong Sheu et al. in 2019 revealed an increased number of DCX-expressing neuroblasts with enhanced dendritic arborization, indicating the surplus amount of interacting neuroblasts in the circuit of the hippocampus in the brains of the maternal immune-activated rodent model of schizophrenia [43]. In corroboration with experimental animal study, they demonstrated an increased level of calretinin-positive cells in the hippocampal DG of postmortem brains of schizophrenia [43]. Notably, an immunohistochemical-based study by Walton et al., reported that the numbers of DCX and calretinin-positive cells were increased in the hippocampal DG of the calcium/calmodulin-dependent protein kinase IIα heterozygous knockout (CaMKIIα-hKO) mouse model of Schizophrenia [204, 208]. Further, they have validated these findings by demonstrating the presence of an increased number of calretinin-positive cells in hippocampal DG of post-mortem brain samples from schizophrenia patients compared to control human brains [204]. Eventually, a large number of postmortem data indicated an increased density of interstitial white matter neurons (IWMNs) in the brains with schizophrenia, which could have been derived from the enhanced production of neuroblasts [209].

Chondroitin sulfate proteoglycan (CSPG) is a key constituent of stem cell niches and an important factor for neuronal differentiation, migration of neuroblasts, and synaptogenesis in the adult brain [210]. Strikingly, studies demonstrated increased expression of CSPGs like neural cell adhesion molecules in the brains of subjects with schizophrenia [136]. Besides, increased levels of NRG1, a key component that interacts with ECM have been observed in postmortem brain tissues and induced pluripotent stem cells (iPSCs)-derived neurons of subjects with schizophrenia [211]. NRG-1 is a crucial molecule that facilitates cell fate determination and neuronal differentiation in NSCs via the ErbB4-mediated signaling cascade [212]. Moreover, elevated levels of growth factors, neurotrophic agents, and cytokines, which play key roles in cell fate in neural progenitor cells and facilitate the differentiation of neuroblasts, can serve as indicative measures of reactive neuroblastosis [213]. Notably, pleiotropic growth factors like transforming growth factor (TGF)-beta and

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metabolic modulators such as peroxisome proliferator-activated receptor (PPAR)-γ have been demonstrated to enhance the number of immature neurons, while their expressions are differential altered in subjects with schizophrenia [29, 47, 213–216]. Hong, S. et al. provide experimental evidence that Poly (ADP-ribose) polymerase (PARP)-1 is required for the differentiation of NSCs, while its absence results in defective neurogenesis and behavioral impairments leading to schizophrenia-like phenotype in experimental animal models [217]. Eventually, altered levels of Wnt signaling components that induce cell cycle events are evident in schizophrenia [75]. A study conducted using iPSCs reported altered Wnt-1 signaling activity in association with abnormal proliferation of neural progenitor cells (NPCs) and altered differentiation of excitatory and inhibitory neurons leading to neuronal circuit miswiring as the developmental origin of schizophrenia [218]. Moreover, subjects with brain metastatic conditions, a state with the malignant proliferation of neuroblasts have been reported to display hallucinations [219]. The animal model of schizophrenia induced by hallucinogenic compounds such as Ketamine and MK-801 (Dizocilpine) has been characterized by an increase in both the quantity and activation of immature neurons in the hippocampus [147, 220]. Notably, the treatment of experimental animals with M108 resulted in an increased amount of neuroblasts and aggravated the symptoms of schizophrenia [43]. As proof of the concept, suppression of the neurogenic process during the adolescent period delayed the onset and progression of schizophrenia-like symptoms in experimental rats [43]. Multiple lines of experimental evidence strongly advocate the intricate relationship between neurogenesis and hallucination in schizophrenia pathology [221].

In the brain, the neuroblasts need to integrate into existing circuits and this process is crucial for proper development and function of the brain. If neuroblasts fail to integrate into existing circuits, they may undergo cell death [222]. Therefore, it can be expected that a surplus generation of neuroblasts would form redundant synapses with existing neurons in a competitive nature. Considering their neurophysiological properties, the variations in the integration of neuroblasts with the existing neural network or retraction of their connections would account for abnormal neuroplasticity in the brain thereby, leading to aberrant neuroplasticity and altered consciousness [44, 223]. Strikingly, neuroblasts have been considered a potential source of the engram, possess electrochemical properties, and exhibit synoptical activities even in an immature state [44, 46, 224]. Engrams are considered to be the biophysiochemical factors generated in the brain that are responsible for cognitive functions, perception, and thinking processes [225]. Recently, abnormal activation of engrams has been proposed as an underlying cause of hallucinations [226] A surplus number of immature neurons resulting from reactive neuroblastosis may tend to integrate into the existing neuronal circuit or may form an extra neural connection in a provocative manner leading to abnormal synoptical, and metabolic activation, thereby drastically misshaping the synapse and electrical events, and creating dysregulation in the release of neurotransmission in the cognitive centers of the diseased brain. Therefore, the abnormal formation of synapses reported in schizophrenia could be associated with differential action potential, neurite outgrowth, and abnormal patterns of synaptic connections during reactive neuroblastosis in the brain [227–229]. The abnormal neurogenic process at the level of integrating an exceeding number of neuroblasts can be proposed to induce abnormal maladaptive behaviors specifically hallucination. Therefore, reactive proliferation and dendritic growth of neuroblasts could potentially be associated with the pathophysiology of hallucination in schizophrenia. While the fate and role of reactive neurblastosis remain unveiled, it is notable that the increased number of neuroblasts tends to be drastically reduced in the end stage of the disease in which depletion of neuroblasts may be associated with dementia. Therefore, the differential modulation of neuroblastosis depends upon the pathogenic or environmental stimuli that could be associated with hallucination and dementia in psychiatric and neurodegenerative disorders (Fig 3). In pathogenic conditions like AD, the neuroblasts tend to express the marker of microglial cells, highlighting their immunological role in the brain [46, 230]. Therefore, further investigation into the mechanisms that drive immunogenic and neurogenic characteristics of neuroblasts in neurodegenerative and schizophrenia contexts could provide valuable insights into the complex interplay between hallucinations and memory loss.
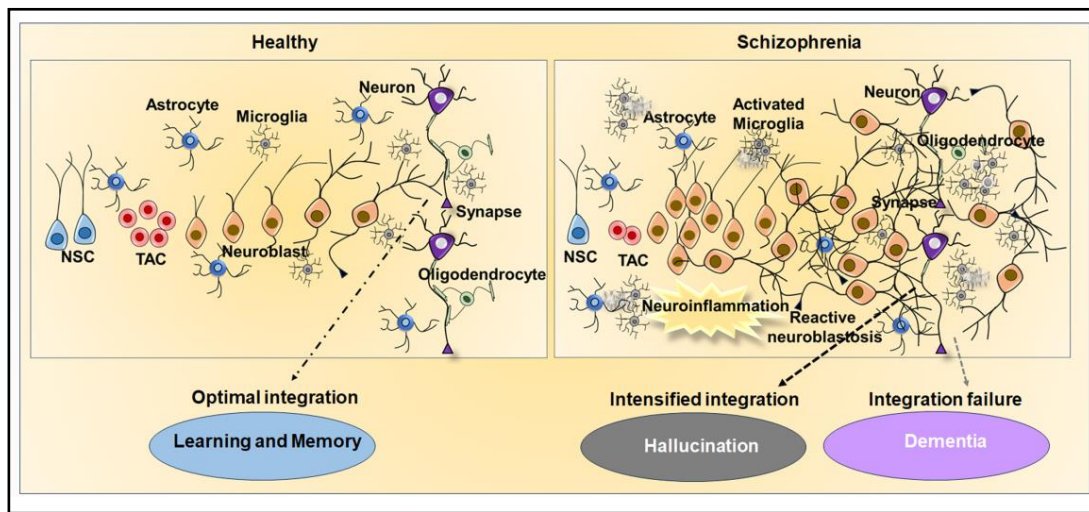
Fig. 3. Regulation of adult neurogenesis and reactive neuroblastosis in health and schizophrenia brains. The picture provides an overview of the neural stem cells (NSC) and transiently amplifying cells (TAC) derived regulation of adult neurogenesis and neuronal integrity in a healthy brain, as well as abnormal neurogenesis and neural integration in schizophrenia. While physiological adult neurogenesis contributes to brain plasticity responsible for cognition function, defective neurogenesis brought on by reactive neuroblastosis causes disruption in neuronal integration and neurotransmission in schizophrenia. Increased neurotransmission from enhanced integration of reactive neuroblasts could be an underlying cause of hallucinations, while decreased neural integration could result in dementia.

Discussion and further direction

The brain is an irreplaceable organ of immense complexity, responsible for synthesizing dreams, imagination, innovative ideas, and a myriad of experiences. Its intricate structure and function majorly rely on neuroregenerative and synaptic plasticity which are driven by both voluntary and involuntary signals. Various functional regions of the brain have a great capacity to spontaneously produce neuroplasticity independent of internal and external stimuli. The key functional areas of the brain have the ability to regenerate throughout life. The regulation of adult neurogenesis mediated by NSCs through the generation of neuroblast have been recognized as a pivotal mechanism underlying diverse cognitive functions, such as intellectual abilities, learning, and memory. Neurogenesis, from development to adulthood, is subject to modulation by a variety of factors. Defects in neurogenesis, particularly at the levels of proliferation and differentiation of NSC and neuroblastosis have been linked to various diseases. Prolonged activation of immune cells can disrupt the neuronal differentiation and integration process of neuroblasts by releasing proinflammatory factors, thereby contributing to cognitive decline, regardless of neuronal loss [34, 47, 151]. Similar to neurodegenerative disorders, schizophrenia has been linked to an aberrant neurogenic process in the brain. Hallucination is the prime behavioral pathology of schizophrenia and subjects with neurological diseases and intake of some drugs induces hallucination for which no confined mechanism has been established. Moreover, the occurrence of dementia has been increasingly evident in schizophrenia [169, 231]. This article emphasizes that reactive neuroblastosis might be responsible for the occurrence of hallucinations as it can abruptly strengthen the synapses and induce abnormal neurotransmission. Besides, failure in the integration of newly generated neuroblasts could contribute to dementia as evidence for neurodegeneration is limited in schizophrenia. Therefore, the futuristic therapeutic targets aimed at harnessing reactive neuroblastosis and correcting the functional integration might be highly beneficial against hallucination and dementia in schizophrenia and other diseases.

With reference to the treatment option, the drugs olanzapine, amisulpride, and ziprasidone have also been implemented to manage the clinical symptoms of schizophrenia and other psychiatric disorders including bipolar disorder. These medications have been linked to the modulation of neurotransmitter systems including serotonin and dopamine which could potentially alter neurogenic process in schizophrenia. Many antipsychotic medications have been shown to have neurotrophic effects by promoting neuronal survival, growth, and synaptic plasticity. For example, preclinical studies have suggested that olanzapine and clozapine enhance BDNF, which could potentially induce neuroblasts to functionally differentiate and effectively integrate into the brain circuit thereby they can harness the reactive neuroblastosis. However, these medications have been known to induce many adverse effects such as movement disorders, seizures, and dementia that are known to be associated with altered regulation of neurogenesis.

Though the turnover of neurogenesis in the human brain and experimental animal brain has been reported to be dissimilar at the level of neuroblast generation, the occurrence of neurogenesis in adulthood has been demonstrated in human brains [184, 232, 233]. In general, understanding the regulation of neurogenesis in the human brain has some drawbacks due to the unavailability of healthy brain samples during the critical period and technical disadvantages [234]. However, the persistence and regulation of neuroblasts have been unequivocally demonstrated in the healthy human brain and aberrant levels of neurogenic process in disease conditions [32, 232, 234, 235]. The reactive neuroblastosis can be investigated using the expression of proliferative markers such as PCNA/Ki67 along with neuroblast markers in postmortem human brains. Eventually, the reporter-based transgenic mouse models that express the marker of neuroblast such as DCX can be subjected to hallucinogenic drugs, and the reactive neuroblastososis can be monitored using live brain imaging and validated by immunohistochemical methods.

Conclusion

Identifying mechanisms underlying hallucination is a fascinating scientific quest in schizophrenia research. While hallucination has been ascertained as the chief psychotic symptom of schizophrenia, the occurrence of hallucination is also increasingly evident in neurodegenerative disorders including AD, PD, and HD. While dementia has generally been attributed to neurodegeneration, recent findings demonstrated that reduced neurogenesis can lead to dementia. Interestingly, schizophrenia has also been characterized by memory loss despite the absence of prominent signs of neurodegeneration. Remarkably, many neurodegenerative disorders have been characterized by reactive neuroblastosis in the progressive pathogenic time frame. While the neuroblasts in the brains have been reported to exhibit electrophysiological properties and serve as a potential cellular resource of engram, abnormal activation of the engrams has been proposed as an underlying cause of hallucination. Therefore, the hypothesis denotes that redundant synaptic connections or their withdrawal from the increased number of neuroblasts may be associated with the generation of abnormal perception resulting in hallucinations. Eventually, failure or defects in the integration of a subset of neuroblasts and their consequent loss could be associated with dementia regardless of the neurodegeneration of existing mature neurons in schizophrenia. While the experimental animal model and few postmortem studies strongly support this hypothesis, adequate human studies are necessary to further validate and understand the role of neuroblastosis in hallucinations. Moreover, the availability of suitable human brain samples, the interference of medication, and methodological drawbacks in assessing the neurogenic process present significant challenges. Presently, the reactive neuroblastosis theory of hallucination provides novel insight into schizophrenia and dementia research, the notion can be further validated with advanced experimental tools and computational

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modelling. By employing cutting-edge techniques such as high-resolution neuroimaging, optogenetics, and single-cell RNA sequencing, alongside sophisticated bioinformatics tools, a deeper understanding of the mechanisms underlying reactive neuroblastosis can be established. The integrated approach would significantly advance our knowledge of the role of neurogenesis in hallucinations and dementia potentially leading to new therapeutic strategies for psychiatric and neurodegenerative disorders.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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