12-2016

The dynamics of adult neurogenesis in human hippocampus

Amadi O. Ihunwo
Aga Khan University, amadi.ihunwo@aku.edu

Lackson H. Tembo
University of Witwatersrand, South Africa

Charles Dzamalala
University of Witwatersrand, South Africa

NEURAL REGENERATION RESEARCH
December 2016, Volume 11, Issue 12
www.nrronline.org

INVITED REVIEW

The dynamics of adult neurogenesis in human hippocampus

Amadi O. Ihunwo*, Lackson H. Tembo, Charles Dzamalala

School of Anatomical Sciences, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

How to cite this article: *Ihunwo AO, Tembo LH, Dzamalala C (2016) The dynamics of adult neurogenesis in human hippocampus. Neural Regen Res 11(12):1869-1883.*

Funding: *This work was supported by the Consortium for Advanced Research Training in Africa (CARTA). CARTA is jointly led by the African Population and Health Research Center (APHRC) and the University of the Witwatersrand and funded by the Wellcome Trust (UK) (Grant No. 087547/Z/08/Z), the Department for International Development (DfID) under the Development Partnerships in Higher Education (DelPHE), the Carnegie Corporation of New York (Grant No. B 8606), the Ford Foundation (Grant No. 11000399), Google.Org (Grant No. 191994), Sida (Grant No. 54100029), MacArthur Foundation (Grant No. 10-95915-000-INP) and British Council.*

Abstract

The phenomenon of adult neurogenesis is now an accepted occurrence in mammals and also in humans. At least two discrete places house stem cells for generation of neurons in adult brain. These are olfactory system and the hippocampus. In animals, newly generated neurons have been directly or indirectly demonstrated to generate a significant amount of new neurons to have a functional role. However, the data in humans on the extent of this process is still scanty and such as difficult to comprehend its functional role in humans. This paper explores the available data on as extent of adult hippocampal neurogenesis in humans and makes comparison to animal data.

Key Words: *adult neurogenesis; neuron; neuronal stem cell; proliferation; differentiation; neuronal turn-over; hippocampus; human neurogenesis*

Correspondence to:
Amadi O. Ihunwo, Ph.D.,
Amadi.Ihunwo@wits.ac.za.

orcid:
0000-0003-1097-7424
(Amadi O. Ihunwo)

doi: *10.4103/1673-5374.195278*

Accepted: *2016-11-18*

Introduction

The phenomenon of adult brain generating new neurons throughout life, known as adult neurogenesis, was considered a postnatal and early life postnatal occurrence. Consequently, loss of neurons in an adult brain was thought to be irreplaceable, a basis for many neurodegenerative diseases (Eriksson et al., 1998; Del Bigio, 1999). The adult mammalian brain, including humans, house neural stem cells (NSCs) in discrete places capable of generating new neurons throughout life. Two regions in adult human brain under normal conditions are confirmed to house NSCs and generate neurons throughout life with certainty. These are subventricular zone (SVZ) of lateral ventricle for olfactory bulb neurons and the hippocampus. Since the first definite confirmation of adult neurogenesis in humans by Eriksson et al. (1998) there has been a substantial number of studies on adult neurogenesis, but questions still remain on the extent of the process and likely functions in humans.

This paper will review the current data on degree of adult neurogenesis dynamics, apoptosis and neuronal turn-over in human hippocampus and compare that to available data on rodents. Jessberger and Gage (2014) highlighted some of the gaps that exist in the current understanding of adult neurogenesis ranging from its regulation, functional to molecular mechanism. To begin to address some of these gaps, the degree of adult neurogenesis process has to be understood. Such an understanding is important to answer if adult neurogenesis has functional implications in humans as observed in animal studies. The hippocampus is a very important structure associated with learning, spatial and episodic memory and mood disorders (Sierra et al., 2011; Snyder and Cameron, 2012). It is therefore important to understand the dynamics of adult neurogenesis in hippocampus. The focus of this review is therefore on the adult hippocampal neurogenesis (AHN) in humans.

Historical Perspective

The inability of the adult brain to generate neurons throughout life was a central dogma in neurobiology. For decades, there was little or no progress for the field. The adult brain was thought to be hard wired and incapable of generating new neurons. A famous neurobiologist, Santiago Ramon y Cajal in 1913 stated "In the adult centres, the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated," (Ramon y Cajal, 1928). And this was in part a reason for slow progress for decades for the field. The complexity of the neural networks in an adult brain affirmed this view, hence new neurons were assumed if added would destabilize the neuronal network (Jessberger and Gage, 2014) as such, it was impossible to integrate the new cells. Incorporation of new neurons was thought that it would destabilize

encoded existing information.

The first hint for occurrence of adult neurogenesis came in 1912 by Ezra Allen. Allen showed mitotic figures in lateral ventricles of albino rats of up to 120 days of age (Allen, 1912; Balu and Lucki, 2009). The progress of the field stalled until in the 1960s when more evidence started gathering. The development of advanced techniques for study of adult neurogenesis rekindles interest for the field and helped to yield a big leap in its progress. The first anatomical evidence for occurrence of neurogenesis in adult rodents was provided by Altman and Das (1965) using auto-radiographic labelling technique. They used a tritiated thymidine, a nucleoside that is taken up in cells that are synthesizing DNA just before the onset of cell proliferation. Altman and Das (1965) observed newly generated neurons postnatally in dentate gyrus (DG) and SVZ and described the migratory path to the olfactory bulb where they become neurons.

However, Altman and Das (1965) study was not immediately accepted by the neuroscience community for two reasons. At that time, there was insufficient evidence that the labelled cells were neurons. Secondly, the labelled cells could have been undergoing DNA repair hence leading to incorrect interpretation of the results. The interest for the field was rekindled in the 1980s. Fernando Nottebohn in 1983, demonstrated that a substantial number of neurons are generated in the song system of adult birds. This gave evidence for synaptic integration of new neurons in song system of adult male song birds, supporting the seasonal learning in male song, hence first evidence for functional integration of adult born neurons (Nottebohm, 1985, 1989; Ming and Song, 2005b; Ahmed et al., 2011).

Later, in 1997 Michael Kaplan collaborated Altman and Das findings using electron microscope by describing cellular phenotype of neurons in mice. The results were purely based on morphological criteria, a factor that was thought as a weakness to accept the findings. Again, the results could not be replicated in primates *i.e*., the rhesus monkey as such it was considered not an occurrence in adult primates (Sierra et al., 2011). Later, Heather Cameron and Elizabeth Gould made a third re-discovery of adult hippocampal neurogenesis in rats. Concurrently, this was the same period bromodeoxyribouridine (BrdU), a nucleotide analogy, which labels mitotically dividing cells was developed. It can be detected using immunohistochemistry (IHC) in combination with several other cell markers for phenotype identification (Ming and Song, 2005b; Sierra et al., 2011). This was a major advancement and a breakthrough in the study of adult neurogenesis. Consequently, it was followed by a substantive contribution to the study of adult neurogenesis.

Broad acceptance of adult neurogenesis occurrence as an integral part of adult brain plasticity was in the late 1990s. To date, adult neurogenesis has been demonstrated in mammals close to man. Over thirteen mammalian taxonomic orders and suborders from different natural environments exhibit evidence for occurrence of adult neurogenesis in hippocampus (Gould et al., 1999; Gould and Gross, 2002; Chawana et al., 2013; Patzke et al., 2015). Some of these are tree shrew, marmoset, rhesus monkey (*Macacamulatta*) (Gould et al., 1998; Del Bigio, 1999), macaque (Kornack and Rakic, 1999; Olude et al., 2014) and African giant rat (Olude et al., 2014). However, earlier studies in rhesus monkey (*Macacamulatta*) reported occurrence of neurogenesis in animals less than 3 years of age, but in older animals, the germinal cells gave rise to glial cells (Del Bigio, 1999). Lack of sufficient sensitivity to detect neurogenesis in older animals was one of the critics for the study. Gould et al. (1998) reported neurogenesis in 3 year marmoset monkey (Callithrix jacchus) and 9–22-year-old rhesus monkeys.

The phenomenon of adult neurogenesis has been reported in humans. Eriksson et al. (1998) gave the first evidence for adult neurogenesis in humans. The study used BrdU to label neuronal progenitor cells, and reported that majority of cells in the subgranular and granular zones of the DG incorporated the BrdU and about 22% of these co-expressed neuronal antigen. Eventually, other studies reported similar findings like Reif et al. (2006) using Ki-67 and more recent an *in vivo* imaging has been used to study adult neurogenesis in humans (Manganas et al., 2007). Spalding et al. (2013b) used ^{14}C technique to birth date mature neurons. The phenomenon of adult neurogenesis has now gained acceptance among neuroscience community and currently is the focus of intense research.

Neurogenic Niches in Adult Brain

Neurogenic niches refer to regions in the adult brain housing NSCs and/or are capable of generating new neurons under normal physiological conditions (Ming and Song, 2005; Balu and Lucki, 2009; Ahmed et al., 2011; Snyder and Cameron, 2012). As mentioned before, in adult mammalian brain, neurogenesis is restricted to the anterior portion of SVZ of the lateral ventricle in olfactory system, and the sub-granular zone (SGZ) of DG in hippocampus (Eriksson et al., 1998; Balu and Lucki, 2009; Ming and Song, 2011; Loi et al., 2014). There exist controversies on other possible neurogenic niches in healthy individuals. These are neocortex, striatum, amygdala, hypothalamus (Balu and Lucki, 2009; Perotin et al., 2009; Sierra et al., 2011), prefrontal cortex (Liu et al., 2008), eye, corpus collosum, optic nerve, spinal cord (Gage and van Praag, 2002) and piriform cortex (Liu et al., 2008; Bofanti, 2016).

Adult neurogenesis has also been induced in diseased or injury conditions in non-neurogenic areas. For instance, in epilepsy, trauma, and dysplasia patients, multipotent NSCs have been isolated from temporal and frontal cortex and amygdala (Sierra et al., 2011). However, the same has not been repeated in healthy individuals. Though this does not mean proof of neurogenesis, it does indicate the altering of the non-neurogenic areas for possible neurogenesis by the disease condition. The presence of only two definitive neurogenic niches in an adult brain raises several questions.

What characteristics do they possess are different from other part of the adult brain to potentiate the NSCs? It is thought in these neurogenic niches there exists a trade-off between structural plasticity and the stability of previous formed connections, which may encode experiences representing or correlate to memory (Knobloch and Jesseberger, 2011). This perhaps explains in part why the entire adult brain does not harbour NSCs.

Olfactory System

In the SVZ, the NSCs are housed in the lateral wall of lateral ventricles in the anterior portion of SVZ. In summary, the quiescent NSCs, extend their cilia into ventricle and contact blood becoming type B cells. Type B cells are eventually activated to proliferate, giving rise to type C cells, which are rapidly dividing cells. This amplifies and creates a pool of new-born cells, which eventually give rise to neuroblasts committed to neuronal lineage (Braun and Jessberger, 2014). The migration of new-born neurons from SVZ to olfactory bulb follows a specific migratory path. The neuroblasts migrate along a rostral migrating system (RMS) (Braun and Jessberger, 2014) through a dense tube of glia cells, a process known as 'chain migration' (Gross, 2000; Balu and Lucki, 2009; Aimone et al., 2010). In olfactory bulb, these new neurons differentiate into distinct subtypes of neurons. The majority are GABAergic granule interneurons or dopaminergic periglomerular interneurons while a few are glutamatergic juxtaglomerular neurons (Lois and Alvarez-Buylla, 1993; Doetsch et al., 1999; Gage, 2002; Balu and Lucki, 2009; Knobloch and Jesseberger, 2011; Braun and Jessberger, 2014).

The neurogenesis process in OB generates a substantial number of neurons but only very limited number survive to integrate, raising doubts about their functional significance. In rodents, an enormous amount of neurons are generated following neurogenesis in OB, however, just a few are integrated into the OB circuit (Braun and Jessberger, 2014). In humans, there is a sharp decrease of neuroblasts in the SVZ after infancy; as such it is suggested that in OB, less than 1% of neurons are exchanged over a century, implying that adult neurogenesis might be of negligible extent (Spalding et al., 2013), though neurogenesis in the SVZ is relatively faster than in the SGZ (Couillard-Despres et al., 2011), posing doubt for functional integration in OB.

Dentate Gyrus in Hippocampus

The DG is one of the structures in the hippocampus located in the temporal lobe of the brain. Found within the DG are broad bands of neurons, which are grouped into SGZ and granule cell layer (GCL). The SGZ is deep to GCL and contains NSCs (Eriksson et al., 1998; Balu and Lucki, 2009; Perotin et al., 2009). The structural appearance of the DG is unique with presence of alternating bands. The DG is seen as having small clusters consisting of dark and light cells, which are in close proximity as seen in semi-thin sections (Perotin et al., 2009). The clusters are homogenously distributed in the neurogenic niche, which is separated from walls of ventricles or ependymal layer (Zhao et al., 2006, 2008; Perotin et al., 2009). The NSCs reside in a layer just about three nuclei wide which include the basal cell band of GCL and two nuclei-wide zone into the hilus (Hastings and Gould, 1999; Gross, 2000; Esposito, 2005; Balu and Lucki, 2009; Perotin et al., 2009).

The NSCs arise and migrate from SGZ into GCL where they differentiate, projecting a large dendritic arbor into molecular layer, extend their axons into hilus terminating on target cells in the hilus and CA3 area after 3 weeks (Braun and Jessberger, 2014) and express neuronal marker proteins (Eriksson et al., 1998; Esposito, 2005; Bonfanti and Peretto, 2007; Bofanti, 2016) eventually maturing into functionary excitatory granule cells (Stanfield and Trice, 1988; Zhao et al., 2006; Toni et al., 2008; Balu and Lucki, 2009). In the DG, the quiescent NSCs also known as type I cells, extend their processes into molecular layer through the GCL. It is activated to give rise to type 2 cells which are non-radial NSPCs, and in turn type 2 cells give rise to neuroblasts, which amplify the neurogenic pool. In the differentiation stage, the neuroblasts begin to branch out processes and migrate up into the GCL (Jessberger and Kempermann, 2003; Zhao et al., 2006, 2008; Braun and Jessberger, 2014), unlike in the SGZ migrating a short distance into the GCL (Couillard-Despres and al., 2011; Bofanti, 2016).

The generated neurons in the DG are of specific type unlike in the SVZ. In the DG, the NSCs generate glutamatergic granule cells, whereas in OB, heterogeneous NSCs give rise to different subtypes of olfactory neurons which later integrate into the OB (Jessberger and Gage, 2014). In DG, the NSCs differentiate into excitatory glutamatergic granule neurons (Jessberger and Kempermann, 2003; Zhao et al., 2006; Knobloch and Jesseberger, 2011). In adult humans, the comparison between OB and hippocampal neurogenesis reveals that there is relatively more neurogenesis in DG than in OB (Gage, 2000, 2002; Gu et al., 2013; Spalding et al., 2013; Jessberger and Gage, 2014).

The Adult Neurogenesis Cellular Processes

Adult neurogenesis processes are complex, elaborate, consisting of distinct phases that are tightly regulated. These phases are proliferation, commitment to neuronal lineage, migration, differentiation (morphological and physiological), integration into the existing neuronal circuit and survival. It also involves cell death through apoptosis, and probably suppression of proliferation of NSCs (Eriksson et al., 1998; Balu and Lucki, 2009; Loi et al., 2014).

Neural Stem Cells and Proliferation

The presence of NSCs in adult brain is beyond doubt, but exact lineage of NSCs is still unclear. The true lineage of NSCs in the neurogenic niches is still under debate. It is suggested that the lineage for NSCs in the neurogenic

niches is not restricted to one type, but a heterogeneous population of precursor cells (Göritz and Frisén, 2012). In the SGZ, it is argued that there are two types of NSCs, both capable of giving rise to migratory neuroblasts, which can later mature into granule cells incorporated into the existing neuronal circuit. Stem cells are defined as those cells capable of self-renewal, able to proliferate and differentiate to other cell progenies (Ming and Song, 2005; Ahmed et al., 2011; Hong et al., 2016). For NSCs in particular, these are cells derived from the nervous system or have the capability to generate neural tissue (neurons and glial cells), possess the self-renewal capacity through symmetrical division, and can give rise to other cell progenies through asymmetrical division (Ming and Song, 2005b; Balu and Lucki, 2009; Curtis et al., 2011; Kitamura and Inokuchi, 2014). The NSCs exhibit high proliferative capacity and multipotency, the characteristic features of stem cells.

The putative NSC is thought to be of astrocytic lineage and is quiescent. It expresses precursor cell marker protein, nestin and has astrocytic properties, *i.e.*, expression of glial fibrillary acidic protein (GFAP) but not S100β (Gould et al., 1994; Kuhn et al., 1996; Reif et al., 2006; Balu and Lucki, 2009; Perotin et al., 2009). In culture, it expresses astrocytic markers and exhibits similar morphological features to astrocytes (Ahmed et al., 2011), suggesting that the source of NSCs are from astrocytic lineage. The astrocytic lineage cells rarely divide rarely but in asymmetrical fashion. Two types of progenies are identified according to morphological properties, both thought to be the source of new neurons in SGZ. These are radial glial cells and non-radial glial cells (Balu and Lucki, 2009; Perotin et al., 2009; Ahmed et al., 2011).

Radial glial cells have triangular soma with thick apical processes reaching and crossing the GCL and branching massively in molecular layer (Ming and Song, 2005b; Perotin et al., 2009), have vascular end feet (Amaral and Witter, 1989; Bruel-Jungerman et al., 2007; Balu and Lucki, 2009) and possess relatively more organelles, polyribosomes, lighter mitochondria as compared to non-radial glial cells (Perotin et al., 2009). They send their thin lateral extensive expansions intercalated between the granule neurons that separate them from neuropile and these expansions are considered as a scaffold during migration of the new neurons in the SGZ (Jessberger and Kempermann, 2003; Amrein et al., 2004b; Zhao et al., 2006, 2008; Perotin et al., 2009). Radial glial cells when activated, give rise to non-radial glial cells, a transient population, which in turn give rise to neuroblasts. Non-radial glial cells have no radial projection, are generally elongated and extend to branched processes parallel to SGZ and thin short secondary branches into the hilus and GCL (Zhao et al., 2006; Perotin et al., 2009). They stain with the antibodies against S-100, a calcium binding protein expressed in some astrocytes and ependymal cells (Perotin et al., 2009), nestin and Sox2 (Dayer et al., 2003; Ming and Song, 2005b; Amrein et al., 2008b; Balu and Lucki, 2009), Tbr2+ (Berg et al., 2015) and are rapidly proliferating (Amrein et al., 2008b; Abdallah et al., 2010; Ahmed et al., 2011; Curtis et al., 2011) with limited self-renewal and further lineage restriction (Balu and Lucki, 2009; Ahmed et al., 2011).

The neuroblasts migrate into GCL where they differentiate into new neurons. They project a large dendritic arbour into molecular layer, and extend their axons into hilus terminating on target cells in the hilus and CA3 area after 3 weeks (Kempermann et al., 2003; Ming and Song, 2005b; Zhao et al., 2008; Braun and Jessberger, 2014) expressing neuronal marker proteins (Eriksson et al., 1998; Bontempi et al., 1999; Bonfanti and Peretto, 2007) eventually maturing into functionary excitatory granule cells (Zhao et al., 2006, 2008; Balu and Lucki, 2009). There are differences in terms of NSCs progeny in SVZ and SGZ. In SVZ, NSCs give rise to a number of subtypes of olfactory neurons, unlike in DG were glutamatergic granule cells arise. It is not clear whether fate differences are intrinsically predetermined or are due to external cues (Knobloch and Jesseberger, 2011; Jessberger and Gage, 2014). Evidence from several studies suggests the interplay of intrinsic and extrinsic cues. For instance, when cultured cells are grafted back, the new-born neurons adopt the fate of the region grafted into, hence external cues influencing the fate (Suhonen et al., 1996; Hastings and Gould, 1999; Jessberger and Gage, 2014). On the contrary, isolated NSCs from dorsoventral axis maintain their site specific characteristics when generating distinct neuronal subtypes in the SVZ (Merkle and et, 2007; Knobloch and Jesseberger, 2011; Sahay et al., 2011) an indication of intrinsic cues at play. It has been argued that such differences could be originating from methodological variations, or that the transplanted NSCs may have been at an advanced stage and just proceeded to their destined fate (Knobloch and Jesseberger, 2011).

Proliferation of NSCs and neuroblasts is not concomitant but follows a stringent control to regulate the neurogenesis process. In animal models, NSCs divide faster than neuroblasts, resulting into a net pool of NSCs (Ming and Song, 2005; Andersson, 2010). In the early stages of adult neurogenesis, strict balance between the NSCs and neuroblasts is a key feature. Some of the factors known to regulate the balance between NSC and neuroblasts are Notch signalling, Wnt signalling, Sox2 transcriptional activity and lipid metabolic processes (Braun and Jessberger, 2014). There is a negative relationship observed between nueroblasts and age. The study by Eriksson et al. (1998) was first to demonstrate occurrence of AHN in humans by observing presence of neuroblasts. It showed possible variations of AHN among the subjects but the results were not conclusive, due to among others, a small sample size of 5, relatively old-aged sample (age range of 58–72 years, mean age of 64.4 ± 2.9 years) and a varied post infusion period from 16 to 781 days. Evidently, the number of detected neuroblasts declined with increased post infusion period as noted by (Nogueira et al., 2014).

Similar results depicting a negative relationship between

age and neuroblasts has been observed by others (Amrein et al., 2004b; Rao et al., 2008; Aizawa et al., 2009; Spalding et al., 2013; Nogueira et al., 2014; Ngwenya et al., 2015). In early part of life, there is a relatively high number of neuroblasts that exhibit a steady decline in later years of life. Ngwenya et al. (2015) reported a 92% reduction of cells labelled with BrdU from rats aged between 32 days and 12 months. Similarly, Rao et al. (2008) observed a decline of 80% in BrdU labelled cells and 85% Ki-67 labelled cells in young and old Fischer 344 rats. Similar results were observed in cynomologus monkeys using Ki-67 (Aizawa et al., 2009). Furthermore, using Ki-67, the DG of the African giant rat showed reduced proliferation from juvenile to adulthood from 12,480 ± 7,860 to 1,130 ± 150 respectively (Olude et al., 2014). A similar pattern is observed in humans. In humans, Dennis et al. (2016) observed a marked decline of adult neurogenesis in the neurogenic niches and that in adult brain there is sparse distribution of proliferating cells which are largely microglia. Comparison of juvenile and adult individuals, showed a drastic decline of proliferative cells in SGZ from juveniles to adults. Using cell densities of proliferating cells (Ki-67$^+$), the ages 0.2, 0.3, 1.0 and > 24 years had 17.9 cells/mm^2, 20.6 cells/mm^2, 3.77 ± 1.39 cells/mm^2 (n = 3) and 0.27 ± 0.18 cells/mm^2 respectively (baseline Ki-67$^+$ density in caudate nucleus = 2.9 ± 2.1 cells/mm^2). Similarly, Bergami et al. (2015) noted that in humans there is a five-fold decrease between 20–100 years. Furthermore, Dennis et al. (2016) observed that the phenotype of proliferating cells changed with age both in SGZ and SVZ. They noted that the distribution of proliferative marker, Ki-67 in juveniles was not confined to SGZ, but was also found in the molecular layer of DG and CA4 region of the hippocampus. In adults, proliferating cells were scarce in SGZ and the adjacent areas.

This declining trend becomes relatively faster in younger animals but steady at some point but during aging, the amount of embryonic generated neurons only remains a declining fraction, slowly been replaced by postnatally generated neurons (Braun and Jessberger, 2014). However, it is not clear at what age for instances 50% of embryonically generated neurons are replaced. Some animal studies observed that the total number of DGCs does not increase with age in rats, while functional integration remains controversial (Ajao et al., 2010; Gu et al., 2012; Spalding et al., 2013). Comparison of proliferation rates between normal and diseased individuals indicates a very interesting phenomenon for adult neurogenesis. Increased adult neurogenesis has been demonstrated in individuals who had seizures, or had suffered from vascular dementia especially in their prefrontal cortices as compared to negative controls. There is preferential proliferation of radial astrocytes in the DG during seizures (Thom et al., 2005). However, in patients with chronic stress, a decrease in adult neurogenesis has been observed (Liu et al., 2008) and in major depressive disorder (MDD) coupled with smaller DG and granule cell layer volumes as observed through stereology (Bergami et al., 2015). This entails that the disease condition alters the neurogenic niches in adult brain.

Affecting proliferation rate of neuroblast is also a life history factor. For instance, in alcoholics the proliferation rate was found to be relatively lower than the age matched non-alcoholic individuals (Andersson, 2010). However, the sample size of 9 with 2 alcoholic cases in Andersson (2010) study, was small to make well-founded conclusions. Despite that this shows the need to investigate how such life history factors affect adult neurogenesis. There are a number of genes required for neuronal maturation. These are Cdk5 and Disc1 (Braun and Jessberger, 2014). The growth of dendrites and physiological maturation is controlled by Disc1 in new DGC (Duan et al., 2007; Zhang et al., 2008), while the survival of adult born neurons is dependent on early N-methyl-D-aspartate (NMDA) (Tashiro et al., 2006; Bergami et al., 2015).

Differentiation and Maturation

The differentiation and maturation process of neuroblasts are a multi-staged process which is tightly regulated. The onset of the differentiation is dependent on the pro-neuronal genes. These are NeuroD1, Prox1 and SoxC transcription factors (Braun and Jessberger, 2014). Also playing a role is the neuronal activity throughout the stages of adult neurogenesis. For instance, excitatory GABAergic inputs activate the NSCs. The NMDA receptors are able to initiate integration of new born neurons into the hippocampal circuit (Braun and Jessberger, 2014). Neuroblasts begin to develop features different from those of NSCs, a characteristic feature for the post-mitotic differentiation period. The new neurons begin to display structural maturation almost after one week with corresponding physiological maturation. In early maturation period (1st week after birth), the new born neurons display high resistance and low membrane capacity. At the same time, the new neurons begin to receive functional y-amino butyric acid (GABA)ergic but not glutamatergic inputs (Ge, 2006; Balu and Lucki, 2009). These maturing neurons are also excited by GABA, crucial for establishment of GABAergic and glutamatargic synaptic inputs and also important for the regulation of the dendritic development.

The electrophysiological pattern characteristic of neuroblasts is complex. Neuroblasts begin to express polysiliated form of the neural cell adhesion molecule (PSA-NCAM), Prox-1, NeuN, calbidin and does not express nestin and Sox2. They also go through a transient expression of DCX and PSA – NCAM and appearance of basal dendrites (Ge, 2006; Balu and Lucki, 2009). Structural and physiological characteristic features precede maturation of post-mitotic neurons. These are rapid elongation of the axon and establishment of appropriate axonal connections within 4–10 days after their birth. Cell clusters for neuroblasts begin to appear as observed from 3D reconstruction studies, suggesting that the neuroblasts clusters sit on a nest of radial astrocytes and this results in making frequent contacts with the mature

granule neurons (Brandt, 2003; Ge, 2006; Balu and Lucki, 2009).

Functional glutamatergic inputs appropriately appear between 14–18 days together with the formation of dendritic spines and continued growth of dendrites (Brandt, 2003; Ge, 2006; Balu and Lucki, 2009). An input-dependent manner regulates survival and incorporation of the newly generated neurons into the existing circuit (Jessberger and Kempermann, 2003; Ge, 2006; Balu and Lucki, 2009). At the end of a 4-week period, the committed neuroblasts differentiate to mature neurons (Sierra et al., 2011; Marques et al., 2016). Ngwenya et al. (2015) observed a delayed migration and maturation of new neurons in young and aged rhesus monkeys adult neurogenesis, but had an approximately 73–76% survival rate. In general, the maturation process takes approximately six weeks with fully functional and integrated neurons into the hippocampal or OB circuit but have different physiological characteristics as compared to those neurones born during embryonic period (Jessberger and Kempermann, 2003; Braun and Jessberger, 2014; Jessberger and Gage, 2014).

The maturation duration for the newly generated neurons varies depending on the species and age of the animal. Neurons mature relatively faster during embryonic development period than in adult animals (Ming and Song, 2011). A comparison of animal species shows varied maturation periods. For instance in rats the maturation period is faster than in mice (Marin-Burgin and Schinder, 2012). Even within the dentate gyrus there is localized differences of neuronal maturation. Local network connectivity is said to likely modulate the neuronal maturation, hence the differential activation of the hippocampal network creates localized domains for newly generated neurons to mature at slightly different rates (Marin-Burgin and Schinder, 2012). Perhaps the question is how is this seemingly unorganised maturation coordinated into an organised pattern?

After the developmental period the newly generated neurons have structural similarities to those generated during the perinatal period but have physiological characteristic differences to those of the perinatal neurons. The adult born neurons display a high input resistance, increased excitability and reduced GABAergic inhibition and physiological characteristics typical of immature neurons (Korbo et al., 2004; Luu et al., 2012; Marin-Burgin and Schinder, 2012; Marques et al., 2016) as compared to prenatal neurons. This is attributed to some functional uniqueness of the newly generated neurons. The maturing neurons in humans express DCX in their cell bodies and processes, and resemble those observed in rodents. Liu et al. (2008) described the DCX positive cells observed in normal and epileptic humans, as having 'no or short uni- or bipolar,' and their cell processes resembled those of the 'A and B' DCX positive cells in hippocampus of adult rodents described by Palmer et al. (2001). Strong labelled and clustering of DCX cells are seen in superficial cortical regions in parahippocampal gyrus (PG) and other regions of the temporal lobe both in normal and epileptic patients.

D'Alessio et al. (2010) also observed in humans morphological changes in DCX positive cells in DG and pyramidal layers in hippocampal sclerosis tissue compared to normal controls. The DCX positive granular cells in normal controls exhibited a typical granular morphology and their somas had high immunoreactivity, with no dispersion among the DG layers. However, in the temporal lobe epilepsy (TLE), an important dispersion was observed and several of the reactive cells were localized into the hilus and into adjacent molecular layers. The DCX positive dendrites in TLE had arborisation that was directed towards the molecular layer, a thing that was absent in the controls and was not observed in Liu et al. (2008) study, due to weak labelling of dendrites hence could not conclude if DCX positive cells in GCL projected their dendrites into the molecular layer. In the pyramidal layer, D'Alessio et al. (2010) observed that in epileptic patients the DCX positive cells in CA1 region, had reactive somas and their apical dendrites were longer with torturous, and many reactive fibers crossed along CA1.

Furthermore, diminishing long chains of DCX positive cells were observed in PG of epileptic patients (Liu et al, 2008) contrary to observations by D'Alessio et al. (2010). Lower staining intensity was observed in epileptic hippocampus as compared to normal controls measured by mean grey value in DG and CA1. Furthermore, lower reactive area for DCX and also a reduced mean number of DCX positive cells in DG of epileptic than normal controls was observed. Liu et al. (2008) concluded that perhaps in epileptic individuals, the DCX positive expressing cells are probably healthy but change their morphology as they proliferate, migrate and differentiate. The genes that control neuronal migration, its integration and subsequent axonal and dendritic extensions are not fully understood. However, the few identified for maturation are cAMP response element-binding (CREB) signalling (Knobloch and Jesseberger, 2011). For neuronal maturation and integration, the following genes are required, Disc1 and Cdk5 (Braun and Jessberger, 2014). Cdk5 and Disc1 (Braun and Jessberger, 2014), growth of dendrites and physiological maturation is controlled by Disc1 in new DGC (Duan et al., 2007; Zhang et al., 2008), while the survival of adult born neurons is dependent on early N-methyl-D-aspartate (NMDA) (Tashiro et al., 2006; Bergami et al., 2015).

Integration of the New Neurones

The newly generated neurons are structurally and functionally integrated into the existing circuit. New neurons formed in the DG have been shown to integrate into the hippocampal dependent learning and memory (Rao et al., 2008; Ming and Song, 2011) though others have questioned the functional aspect (Ajao et al., 2010; Spalding et al., 2013). In humans, there is almost no direct data to demonstrate the functional integration of the new neurons as such its function is largely

inferred. The newly generated neurons play a role in the information processing, but one critical determinant is the required period for maturation and functional integration (Marin-Burgin and Schinder, 2012; Bowers and Jessberger, 2016; Marques et al., 2016). Structural and functional integration of the new neurons takes relatively a longer period. After a prolonged period of maturation, mature adult born neurons, exhibit similar electrophysiological properties like older neurons in adult brain. New neurons are 'specifically selected' for integration which is dependent on activity based (Knobloch and Jesseberger, 2011).

The maturation and integration process involves, firstly, tonically activation of the new neurons by ambient GABA which is released from local interneurons. This is followed by GABAergic inputs and finally glutamatergic synaptic inputs and mossy fibres synaptic input to hilar and CA3 neurons (van Praag, 2002; Schmidt-Hieber et al., 2004; Ming and Song, 2005; Wiskott et al., 2006; Zhao et al., 2008). These new neurons exhibit a relatively hyper-excitability and enhanced synaptic plasticity during specific developmental stages (van Praag, 2002; Kobayashi and Poo, 2004; Ming and Song, 2005; Kitamura and Sugiyama, 2006; Wiskott et al., 2006; Zhao et al., 2008).

Cell Apoptosis

Cell apoptosis in AHN is extensive, yet its role is speculative. Cell apoptosis refers to a process a cell undergoes resulting into distinguishable physiological and morphological changes leading to the death of the cell. Neurons are created in excess (Balu and Lucki, 2009; Abdallah et al., 2010; Aimone et al., 2010; Ajao et al., 2010; Ahmed et al., 2011; Knobloch and Jesseberger, 2011) thereby creating a relatively large pool of proliferating cells that eventually undergo apoptosis. There is a significantly large number of neurons that undergo apoptosis, a process that was initially thought as an occurrence mainly during embryonic period (Loi et al., 2014), with the surviving cells migrating into GCL using radial glia scaffold as observed in animal studies. It is now known to be a common phenomenon after some time of a lesion. It is important for faulty NSCs to be promptly removed and as a quality control measure considering the multipotency of NSCs (Yuan and Yankner, 2000; Sun, 2004; Hong et al., 2016).

At population level in the DG, there is relatively a large number of neurons modulated each month. About 6% of the total population of the DG neurons are modulated per month (Gu et al., 2013; Hong et al., 2016). During this process, the majority of the generated neurons do not survive. A significant number of neurons die. Approximately 50–80% of newly generated neurons undergo apoptosis (Balu and Lucki, 2009; Gu et al., 2012; Snyder and Cameron, 2012), while survival of the rest is dependent on a number of factors as highlighted by Zhao et al. (2006). Between weeks 1–3, the survival of neurons is promoted mainly by animal's experience such as learning and exposure to enriched environment (Zhao et al., 2006; Kee et al., 2007; Tashiro et al., 2007). In week 3, the signaling through NMDA receptor also promotes the survival of the neurons and do coincide with the formation of dendrite spines and functional glutamatergic inputs (Zhao et al., 2006).

Apoptosis has a functional role, though is it still speculative. Cell apoptosis occurs once the cells are post-mitotic and express both DCX and calcetinin. Cell apoptosis is thought as a mechanism of balancing net proliferation rate and a mechanism of removing damaged cells (Eriksson et al., 1998; Balu and Lucki, 2009; Snyder and Cameron, 2012; Loi et al., 2014) and is not confined to embryonic period in mammals. This elimination process of cells is rapid hence the number of new cells remains stable 2–3 weeks after exiting cell cycle (Oppenheim, 1991; Naruse and Keino, 1995; Robinson and Kolb, 1997; Balu and Lucki, 2009; Curtis et al., 2011; Snyder and Cameron, 2012). Apoptosis counterbalances the continuous adding of new neurons through adult neurogenesis (Zupanc, 1999; Imayoshi et al., 2008; Hong et al., 2016). Through apoptosis, a functional pool of NSCs is maintained, however accelerated death of NSCs or reduced generation of NSCs will hinder neurogenesis (Hong et al., 2016). When compared to necrosis, apoptosis is a controlled and better process of cell death as there are no side effects associated with necrosis (Zupanc, 1999) and is preferred mechanism after some time of a lesion.

The rate of apoptosis in animals is affected by endogenous and exogenous factors. Enriching the environment affects the rate at which apoptotic cells are removed from neurogenic environment. Under basal conditions in adult brain, the apoptotic neurons are quickly phagocytised from the neurogenic niches by the un-activated microglia (Zupanc, 1999; Yuan and Yankner, 2000; Ming and Song, 2011). In contrast enriching environment by melatonin reduces the rate of apoptosis. For instance, in post ischemic group of rats, neuronal apoptosis was reduced in 72 hours and 7 days after environment enrichment with melatonin (Ajao et al., 2010). This indicates a need to thoroughly understand neuronal cell apoptosis in humans for possible modulation.

The extent of DG neurogenesis and neuronal turn-over

The neuronal turn-over rate is the rate at which neurons are exchanged at population level. In hippocampus, there exist two different types of neuronal populations, one that turnover continuously and the other that do not Spalding et al. (2013). The size of the renewing cell population exhibits variations when compared across species. In human hippocampus, about one third of neurones are subject to exchange. This is in contrast to the thinking that a small insignificant number of neurons are exchanged in order to preserve memory by maintaining a stable population (Snyder and Cameron, 2012). In human hippocampus, the renewing cell population is relatively bigger as compared to rodents for instance. The renewing population consist of about 35% [95%*CI* (12–63%)] of DG neurons in contrast to 10% in DG of in adult rodents that undergo neuronal

exchange.

It is reported that at least 700 neurons or 0.004% of the DG neurons are added daily in each human hippocampus translating to neuronal turn-over of 1.75% of neurons in adulthood within the renewing fraction (Spalding et al., 2013), but exhibit an age dependent decline that parallel the decline of neuroblasts (Eriksson et al., 1998; Bergami et al., 2015; Bowers and Jessberger, 2016). This suggests that all the neurons in DG will turnover in adult hippocampus with half of the neurons undergoing apoptosis as explained above. In 3 months old rats, the number of neuron generated are quite extensive *i.e.*, greater than 650,000 granule cells (Snyder and Cameron, 2012). Even in older rats, there is a substantive number of neurons generated *i.e.*, in 2-year-old rats, which has surpassed the life expectance of rats, 50,000 young neurons were reported to be found (Snyder and Cameron, 2012).

One has to be cautious when interpretation and making comparison of such data. One reason being that the methods used and markers are not necessarily the same, hence this could introduce some inherent differences. Furthermore, data from immunohistochemical images only provide a snapshot of a point in time of the adult neurogenesis process, since it labels neurons transiently during the expression of the endogenous markers (Snyder and Cameron, 2012). A number of studies have used DCX and TUC-4, to depict the decline of adult neurogenesis. These two markers do not capture the survival rate of newly generate neurons as they exhibit drastic reduction with age (Snyder and Cameron, 2012). It is therefore imperative to be cautious when making such comparisons and conclusions.

Comparison of renewing fraction to non-renewing population shows that the renewing population is relatively smaller. The renewing population comprise of an average of 51% [95%*CI* (22–88%], and a median annual turnover of 3.5% but exhibit an age dependent decline (Spalding et al., 2013). The renewing fraction in the DG seems to increase with age. The neuronal number in DG is least affected, indicating a relative increase in the proportion of renewing fraction (Bergami et al., 2015). Within the renewing fraction, there seem to be a preferential loss of adult born neurons. Adult born neurons die faster through apoptosis as compared to neurons born in early stages (Oppenheim, 1991; Yuan and Yankner, 2000; Bergami et al., 2015; Bofanti, 2016). Evidently, cumulative studies of postnatal neurons, indicate that there is a net increase of generated neurons with age. The total number of neurons increase with the advancing age. It is reported that the population of the post-natal neurons increase to as close as twice as large in number, approximately 40% of the total population by the end of animal's life span (Amrein et al., 2004b, 2008; Snyder and Cameron, 2012; Ngwenya et al., 2015).

Evidence from stereology studies, has given a good comparison of the turnover rates for a few animal species. In humans, about 0.004% are exchanged per day (Spalding et al., 2013), while in 2-month-old mice it is 0.03% to 0.06% and for the 5–16 year old macaque it is 0.04% per day (Bergami et al., 2015). Between the ages of 2–9 months, mice experience a 10-fold decline in neurogenesis, in comparison to 4–5 -fold decline in humans (Bergami et al., 2015; Bowers and Jessberger, 2016). The comparison of macaque relative rate of neurogenesis to rodents, reveal an approximately 10-times fold lower rate of adult neurogenesis in macaque than rodents (Bergami et al., 2015). However, the majority of the cells born became neurons similarly in rodents. Elucidating from mice studies, this perhaps supports the functional aspect of neurogenesis and by extension, also in humans. It is not known if the reported decline in neurogenesis correlate with decreased cognitive function as noted by Bowers and Jessberger (2016).

Comparing the rate of adult neurogenesis between young and old, the rate of neurogenesis in older macaque was lower than in young macaque and decreased linearly with age (Bergami et al., 2015). The decline occurred just before the onset of midlife and is comparable to that observed in rats and mice. Despite the reported decline of the neurons generated with age, the cell cycle is said to be unchanged with the advancing age (Snyder and Cameron, 2012).

Adult neurogenesis decreases with age which correlates with a lack of measurable growth of the DG later in life. From rats studies, evidence suggest that deceased adult neurogenesis is due to a combination of factors. Among them are large decrease in proliferation, slowed migration of cells from SGZ to GCL and reduction of cell differentiation into neuronal phenotype (van Praag, 2002; Sun, 2004; Song, 2005; Thom et al., 2005; Zhao et al., 2006; Balu and Lucki, 2009; Georg Kuhn and Blomgren, 2011; Satvat et al., 2011; Snyder and Cameron, 2012).

There are currently methods and techniques available to measure the extent of neurogenesis in humans. In rodents, the extent of neurogenesis has largely been measured using histological techniques such as thymidine analogs, retroviral vectors which selectively label dividing cells and their progeny, transgenic markers expressed in NSC, neuroblasts, transgenesis-based lineage tracing (Bertaina-Anglade et al., 2000; Biebl et al., 2000; Jessberger and Kempermann, 2003; Amrein et al., 2004b; Jessberger and Gage, 2014).

Factors that have a regulatory effect on adult neurogenesis

Adult neurogenesis is regulated or modulated by exogenous and endogenous factors. These factors up-regulate or down-regulate cellular processes of adult neurogenesis. From animal studies, changes in hippocampal volume have been correlated to other factors, suggesting that changes observed in the hippocampal volume relates to increase/decrease in hippocampal neurogenesis (Bergami et al., 2015). Some of these factors are enriched environment, behavioural, stress and depression, genetics and growth factors, disease, neuroendocrine early life experiences, physical exercise and neurochemical factors.

Growth Factors

Growth factors generally have an up-regulatory effect on adult neurogenesis. Proliferation, lineage choice of NSCs and differentiation of neuroblasts, are generally up-regulated by a number of growth factors. Increased levels of neutrophilic factors, such as fibroblast growth factor-2 (FGF-2), brain derived neutrophilic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) are associated with high neuronal proliferation (Rao et al., 2008). The response to growth factors is not uniform in the neurogenic niches. Increased EGF and FGF-2 infused intracerebroventricular in adult rats, increase proliferation in SVZ but not in DG (Gage, 2002; Erickson and Barnes, 2003; Esposito, 2005). This selective response in SVZ and DG is peculiar and indicate the need to thoroughly understand how such factors alter adult neurogenesis in health and unhealthy individuals.

Stress and depression

Stress and depression are known to have a down-regulatory effect on adult neurogenesis. Structural and functional aspects of the adult brain are genetically determined, but early life experiences, modulate the maturation and how the brain will cope with adverse events, among them, stress (Loi et al., 2014). From animal studies, exposure to acute stress suppresses one or more phases of adult neurogenesis. As such increased vulnerability to stress is related to decreased rate of adult neurogenesis (Loi et al., 2014). In rodents, the pathophysiology of stress and hippocampal volume reduction are associated with structural impairment, including reduced adult neurogenesis (Loi et al., 2014). In marmoset monkeys decreased cell proliferation is associated with exposure to stressful events (Gage, 2002; Lafenetre et al., 2011; Marques et al., 2016). Early life adversity negatively affected the brain structure and function, but this is normalized by an enriched environment (Loi et al., 2014). Therefore, prolonged negative life experiences, could be a confounding factor in interpretation of adult neurogenesis data if the organism experienced it.

In humans, stressful events have been indirectly shown to have an effect on adult neurogenesis. Cognitive deficit has been observed in depressed patients, and this is concomitant to reduced hippocampal volume. Some antidepressants are also known to enhance adult neurogenesis. Examples are fluoxetine (Braun and Jessberger, 2014). Again, maturation period of newly-born neurons, mirror the period anti-depressant exert their therapeutic effect, suggesting that perhaps it also in part enhance neurogenesis (Braun and Jessberger, 2014). Lastly, most of the anti-depressant drugs reduce or normalise reduced adult neurogenesis, and behaviour responses corresponding to anti-depressant drugs are usually disturbed by disruption of adult neurogenesis (Loi et al., 2014).

Interestingly, stress and corticoids both have similar effect on adult neurogenesis, the same way endogenous glucocorticoids have on angiogenesis. Stress inhibits proliferation of neuroblasts in DG, so is increased levels of glucocorticoids on neuroblasts proliferation (Starkman et al., 1999; Czeh et al., 2001; Gage, 2002). Reversing the condition by reducing serum glucocorticoids by adrenalectomy, elicits cell division in DG (Starkman et al., 1999; Hayashi et al., 2004). Likewise, VEGF is associated with angiogenesis in brain, but is also up-regulated by anti-depressants. This suggests the possibility that neurogenesis and angiogenesis processes in the adult DG could be either parallel phenomenal or/and have functional linkages (Andersson, 2010).

Inherent traits

Inherent traits have an influence on proliferation and differentiation of the progenitor cells. Proliferation, differentiation of NPCs and maturation of new neurons are dependent and separately influenced by inherent traits. Inherent traits introduce variations in adult neurogenesis dynamics. For instance, in different mice strains, proliferation and survival rates of neurons were different (Gage, 2002; Ge, 2006), though they are in turn modulated by other factors like environment, behaviour and biochemical factors.

Microenvironment

The microenvironment or neurogenic niche has an influence on adult neurogenesis dynamics. The neurogenic niche is made up of cells, molecules and structure that allow occurrence of proliferation and neurogenesis in certain places while restricting the same in other parts of the adult brain. The following are the components of the neurogenic niche; endothelial cells, ependymal cells, astrocytes and microglia, mature neurons and vascular components (Rao et al., 2008). Cellular dynamics exhibit corresponding fluctuations dependent on DG neurogenic niche (Rao et al., 2008), hence it acts like a 'dynamic' structure which allows a sphere of interactions for NSCs and its environment, and consequently alters the location and characteristics of the NSC (Ahmed et al., 2011). For instance, dense clusters of proliferating cells have been observed to associate with vascular structures and cerebral spinal fluid (CSF) in SGZ (Ming and Song, 2011). In *in vivo* studies, it has been demonstrated that neurogenic niches have a functional control over neuronal development (Ming and Song, 2011). The neurogenic niche has been widely described in mice but modifications in other mammals have been observed.

Enriched environment

Enriching the environment has an up-regulatory effect on adult neurogenesis. In adult DG, recruitment of NSCs and its fate in differentiation is affected by the organism's behaviour in its enriched environment (Gage, 2002; Andersson, 2010; Loi et al., 2014). Melatonin has positive effect on the rate of adult neurogenesis. Administering melatonin prior to ischemia, enhances adult neurogenesis in the DG (Ajao et al., 2010). A better understanding of how enriched environment modulate adult neurogenesis will be of great potential in enhancing animal's behaviour. The regulatory

effect of environment on neurogenesis also offers an opportunity to study the interaction between nature and nurture (Gage, 2002).

Age

Age is another important factor affecting or altering adult neurogenesis. In humans and other mammals, neuroblasts are available the entire lifespan but exhibit an age dependent decline (Gage, 2002; Friedman, 2008; Rao et al., 2008; Andersson, 2010; Ming and Song, 2011; Bergami et al., 2015), which in part, could be due to increased levels of glucocorticoids (Gage, 2002). In aging rats, the process of adrenalectomy reverses the age related decline of NPCs proliferation due to decreased levels of glucocorticoids. In humas, it is still not clear as to what are the dyanamics of adult nurogenesis across the life span. There has been very limited attention on the extent of adult neurogenesis across life span. It is very important to deepen our understanding on the extent of adult neurogenesis process in humans from pre-adolescent to late adulthood, and how other factors like sex, life experiences (alcoholism, sedentary/non-sedentary life style, *etc.*) alter the process.

Hormones

Steroid hormones have an effect on adult neurogenesis. For instance testosterone in birds, enhances adult neurogenesis while estrogen exhibits a transient proliferation (Gage, 2002). Insulin also plays an important role in hippocampal development and its function. Therefore, insulin is critical for the survival and proliferation of NSCs and neurogenesis in the hippocampus (Hong et al., 2016).

Diseases

Some diseases and other neuropsychiatric conditions alter adult neurogenesis dynamics, by either increasing or decreasing its rate. Increased proliferation has been observed in Huntington's disease (HD), ischemic lesions in the neurogenic regions while reduced or impaired neurogenesis has been observed in other neurogenic conditions such as Parkinson's disease and Alzheimer's disease (Jin et al., 2004a, b; Knobloch and Jesseberger, 2011). The question of would altered neurogenesis cause disease(s) is another important question for the neurobiology community (Knobloch and Jesseberger, 2011). This information has been largely obtained from animal models *i.e.*, rodents. The decreased adult neurogenesis in diseased conditions is due to two main factors. Firstly, there is reduction in neuronal activity or survival, secondly altered neurogenesis leads to aberrant maturation hence resulting in abnormal maturation and integration (Braun and Jessberger, 2014).

From experimental animal models, insults to the brain like, seizures, alter the rate of granule cell neurogenesis. For instance following pilocarpine-induced status epilepticus and kainic acid-induced seizures in adult rats, the rate neuroblasts migration is increased and cell proliferation has been observed to peak after three days following seizure before declining again (Thom et al., 2005).Using an indirect marker for cycling cells, the mini chromosome maintenance protein 2 (Mcm2), Thom et al. (2005) observed higher number of Mcm2 positive cells in the dentate gyrus (mean density 16.4/mm^2) in hippocampal sclerosis (HS) in normal humans than in controls. Similar results have previously been reported using Ki-67 but with low volume of 1.0 to 1.5/mm^2. One of the reasons for such differences has been noted as MCM detect a larger portion than the Ki-67. The Mcm2 detect all stages of cell cycle and those with potential to proliferate unlike the Ki-67 which detect cyclin stages of a cell. .

Altered hippocampal neurogenesis is one of the key characteristic features in the temporal lobe epilepsy (TLE) with hippocampal sclerosis. Both epileptic and normal individuals exhibited DCX positive and strongly labelled cells in temporal cortex (Liu et al., 2008; D'Alessio et al., 2010). Comparison of DCX positive cells, showed a significantly higher DCX positive cells in epileptic individuals than the normal individuals as shown through Western blot method (Liu et al., 2008). However, Fahrner et al. (2007) observed a negative relationship between DCX expressing cells in normal and epileptic patients, which Liu et al. (2008) concluded that the significant increase in DCX expressing cells in epilepsy as compared to normal individuals was possibly due to epilepsy and not effect of age as concluded by Fahrner et al. (2007). This perhaps suggest that the epilepsy do up-regulate the normal process of neurogenesis. Liu et al. (2008) and D'Alessio et al. (2010) found conflicting results on DCX expression in temporal lobe. D'Alessio et al. (2010) reported a decreased DCX expression in hippocampus in epileptic patients as compared to normal controls, with significant reduction observed in CA1 and DG regions. Liu et al. (2008) used hippocampal homogenates, while D'Alessio et al. (2010) observed DCX expression after therapeutic lobectomy of patients with TLE. The effect of various disease conditions on adult neurogenesis has been reviewed elsewhere (Thompson et al., 2008; Lazarov et al., 2010).

Therefore, a thorough understanding of regulatory factors for AHN is important for its application. As noted by Ming and Song (2011), adult neurogenesis is a well-regulated process, but can be modified or modulated by physiological, pathological and pharmacological factors. Therefore, a better understanding of cellular dynamics, mechanism and factors modulating adult neurogenesis process will eventually offer an opportunity to realize the full potential of adult neurogenesis in public health and for societal benefit.

How is process of adult neurogenesis regulated?

Despite the complexity of the neurogenesis regulation, the process is slowly being understood, though a lot need to be done. The neurogenesis process in adult brain unlike in embryonic period is asynchronous process, where neurons are at different stages of development (Knobloch and Jesseberger, 2011). There is contribution of both intrinsic and extrinsic factors in regulating adult neurogenesis. It is

thought that the interplay of intrinsic and extrinsic cues regulate NSCs, however as to how it is regulated and to what extent each contribute is still not clear (Knobloch and Jesseberger, 2011). In regulating NSCs activities, the key mechanism factors are transcription mediated through for instance SOX2, NeuroD1, PAX6, GSX2 and Prox1, and epigenetic mechanism acting through for example histone modification (*e.g.*, MeCp2 and MDB1) and also non-coding RNAs (*e.g.*, miR-24). Moche-derived morphogens, neurotransmitters, growth factors and cytokines are also important factors controlling NSCs activity and neuronal differentiation (Jessberger and Gage, 2014). These include gamma aminobutyric acid (GABA), glutamate, brain derived neurotrophic factors (BDNF), epidermal growth factor (EGF), fibroblast growth factor (FGF)-2, Wnt ligands, Shh, BMP, interleukin (IL)-6 and tumour necrosis factor alpha (TNFα). As discussed above two of the epigenetic factors sex and ageing down-regulate adult neurogenesis while physical activity, environmental enrichment, and learning and memory up-regulate the adult neurogenesis process (Lafenetre et al., 2011). There is also evidence suggesting that network activity directly affecting neurogenesis process in DG and SVZ as observed in rodents (Jessberger and Gage, 2014).

Prospective Benefits of Adult Neurogenesis

There is great potential for possible application through modulation of adult neurogenesis process from other fields. For instance, psychologists and behavioural neuroscientists are focusing on mechanisms by which adult neurogenesis maintains or improves cognitive processes, such as short- and long-term memory, while clinicians are fascinated by the prospect of repairing damaged neuronal tissue and functions (Rao et al., 2008; Rotheneichner et al., 2013; Spalding et al., 2013). However, such potential application, will be a distant dream if the whole process of adult neurogenesis is not fully understood as noted by Rotheneichner et al., (2013). The information on functional aspect of adult neurogenesis is mainly from correlation studies and those that selectively deplete neurogenesis. At the moment there is no gold standard to test the functional aspect of the newly generated neurons more especially in humans (Knobloch and Jesseberger, 2011).

Therapeutic application

Harnessing the NSCs for potential use in therapeutic application to CNS related diseases is one of expected future outcomes. The presence of the NSCs in the human brain has raised hopes for endogenous repair for altered brain integrity through activation and targeting of NSCs (Jessberger and Gage, 2014). Potential use of NSCs would include, but not limited to the following; transplantation to repair diseased, injured or missing neuronal cells, activation of endogenous neuronal cells to provide self-repair (Gage, 2000) and also modulating the process to eradicating stress symptoms Rotheneichner et al. (2013). The use of NSCs will not be restricted to known neurogenic niches, but also from other regions of the brain. The NSCs from other brain regions have been isolated and are able to give rise to neurons with high levels of FGF-2 (Gage and van Praag, 2002). These NSCs are able to survive in the brain after been grafted back, however, fate of grafted cells depends on the local environment (Gage and van Praag, 2002).

Culturing of neuronal cells from adult rodents and human tissue has become a common routine recently. Palmer et al. (2001) observed increased proliferative activity in cultured neuronal tissue from a 27-year-old human and an 11 week- old postnatal male when FGF-2 and its stem co-factor, the glycosylated form of cystatin C were added to the cultures and this in turn greatly improved the survival rate and growth of neurons. These cultured tissues were from ventricular zone, motor cortex, and corpus collosum and hippocampus. Interestingly, all the cultures gave rise to progenitor cells but greatest yield was observed in the hippocampus and ventricular zone. All cultures had spontaneous proliferation and produced relatively similar proportions of neurons and astrocytes, but number of spontaneous neuronal generations were slightly lower in fetal than adult cultures but decreased significantly as the cultures reach senescence. The rates of population doubling were different between cultures from 11-week-old postnatal male and the 27-year- old, before showing signs of senescence. For the 11-week-old postnatal male, the culture grew at log phase for more than 70 population doublings while the 27 years old had 30 population doublings. Tissue from 11-week-old postnatal male yielded significantly more cells/gram and had a higher proliferative capacity. However, these properties were affected by intrinsic growth factors, as observed when differentiation was induced by withdrawing growth factors while stimulating cells with Forskolin and Retinoic acid.

Neurospheres, which are free floating spheres formed from NSCs and can be grafted back in an organism body, have ignited the prospects of using NSCs in therapeutic applications. Neurospheres have been isolatedand cultured from striatum and other brain regions that are not neurogenic, and are able to give rise to neurons or glia as observed from rodents' studies (Amrein et al., 2008, 2011). These are promising results from transplantation studies in animal models. In stroke animal models, endogenous NSCs can migrate to lesion site and differentiate into neuron. In transplantation studies, the NSCs are able to differentiate into neurons within the lesion and also promote the survival of the newly generated neurons (Duan et al., 2007; Braun and Jessberger, 2014).

Enriching cognitive performance

The hippocampus is a very important structure in the hippocampal-dependent behaviour function of the brain. Most of the studies examining the function of the DG have largely been done on the whole hippocampus. Specifically, the DG is involved in the pattern separation, spatial learning and

memory and balancing between memory consideration and forgetting (Jessberger and Kempermann, 2003; Braun and Jessberger, 2014; Bowers and Jessberger, 2016). Enriching cognitive performance is a prospective adult neurogenesis benefit. Enhancing adult neurogenesis promotes better performance in spatial learning tasks as observed in animal studies. For instance, housing mice on running wheels enhanced neurogenesis which was followed by an improved performance on water maze tasks as compared to sedentary mice. Factors like ageing and stress have been correlated with decreased neurogenesis hence reduced performance in the water maze in mice (Braun and Jessberger, 2014; Bowers and Jessberger, 2016). Evidently, ablation of new neurons in hippocampus, is associated with contextual and spatial memory deficit (Ahmed et al., 2011), suggesting a functional role of the new neurons in cognitive plasticity. However, enriching environment restored some neurogenesis and produced improved performance on water maze tasks.

It is worth noting that it is not known if voluntary exercise would have similar results in animals let alone in humans. Our observation in the Long-Evans rats exposed to running exercise indicates that this is true. However, this probably suggests that the hippocampal dependent learning and memory can be enhanced through enhancement of adult neurogenesis. Despite the evidence for functional integration of new neurons into hippocampal dependent learning and memory in rodents for instance (Rao et al., 2008; Ming and Song, 2011), such findings have been questioned (Ajao et al., 2010; Spalding et al., 2013). There are strong associations between new born neurons and region specific cognitive tasks as studied through genetic gain and loss functions. It is understood that the behavioural pattern separation requires new neurons (Jessberger and Kempermann, 2003; Jessberger and Gage, 2014). Pattern separation is the ability to transform similar inputs or experiences into distinct and non-overlapping representations (Braun and Jessberger, 2014; Jessberger and Gage, 2014). On the contrary, the new neurons have also been associated with the forgetting of previous acquired memory (Jessberger and Gage, 2014).

Adult born neurons and prenatal born neurons have different thresholds. New born neurons have a low threshold, as such a smaller stimuli is needed to elicit plasticity associated responses in new born neurons. It is suggested that the low threshold is necessary to distinguish highly similar inputs and overtime transform the information into highly specific representation (Jessberger and Gage, 2014).

Adult neurogenesis dynamics in humans

The study by Spalding et al. (2013) observed the dynamics of AHN through C14 dating technique. It observed negative association between AHN and age. However, the method used observed only mature neurons and could not provide information of neuroblasts proliferation and differentiation. Andersson (2010) reported similar results but observed relatively lower neuroblasts in alcoholics than age matched non-alcoholics. But this study had 9 subjects with 2 alcoholics, making the findings not conclusive. Manganas et al. (2007) observed neuroblasts and described an age dependent decline from preadolescence (8–10 years old) to adulthood (30–35 years old) in humans using a magnetic resonance spectroscopy (MRS) technique, but the validity of the results has been questioned. Firstly, the use of MRS and a complex formula, of which the researchers were 'inexperienced' probably, invalidated the *in vitro* data which in the end, resulted in the unwanted analytic processing in *in vivo* (Friedman (2008). Furthermore, the use of a specific biomarker, whose peak was overlapping with non-specific lipid raised questions for the validity of the results (Jansen et al., 2008). In addition, the specific biomarker could probably vary in health and diseased individuals and also from different regions of the brain.

Evidence suggest that age-dependent changes in AHN in many mammalian species are species-dependent (Amrein et al., 2004a, b, 2008) and reflect down-regulation rather than just a developmental loss-of-function (Balu and Lucki, 2009; Loi et al., 2014). A study from Spalding et al. (2014) showed that every day a considerable amount of neurones are generated. Coupled with ageing, the DG is composed with reduced fraction of neurons generated during embryonic period and are gradually replaced with those born postnatally (Braun and Jessberger, 2014).

In humans, an age-dependent decrease of AHN has been described by biochemical measures (Fahrner et al., 2007), chiefly because the number of discovered dividing cells in post mortem brains appeared very low. From these data, one can expect very low or missing adult neurogenesis after the age of 40 years, and some proliferation activity in brains of children. Seress et al. (2001) concluded that the majority of dividing cells in infants under one year of age is comprised of glial cells, but could not quantify this because of lack of markers for young neurons. On the other hand, these findings are in contrast with the observation about decent AHN in terminally ill elderly patients (Eriksson et al., 1998). This discrepancy may reflect the use of highly dosed (and toxic) BrdU labeled dividing stem cells in the sick patients in a previous study (Eriksson et al., 1998). Secondly, comparisons of animal data with post mortem human material are not possible because all human data are derived from a few sections only, or are given in area or density measurements. Thirdly, comparing rates of neurogenesis and apoptosis makes sense only when the total population of granule cells of the individual is available. This is not even the case for a single human brain, lest to speak of the situation at different age levels.

Conclusion

The phenomenon of adult neurogenesis occurrence in humans is an accepted event. Olfactory system and hippocampus retain the capacity to generate new neurons throughout life. In hippocampus, the putative NSC is thought to be of

astrocyte lineage, and following proliferation gives rise to significant amount of neuroblasts, however almost half of neuroblasts undergo apoptosis. The extensive apoptosis of the generated neurons is thought as a mechanism of balancing and maintaining the neurogenic pool, important for the maintenance of adult neurogenesis. In humans, there are a substantial number of neurons generated. In comparison to rodents, in humans there is a 4-fold increase in neuronal generation. However, both animals and humans depict a drastic decline of neurogenesis when examined across the ages from juvenile to adulthood. The rapid proliferating rate during infancy could perhaps correlate to cognitive development of the organism. The field of adult neurogenesis has generated a lot of interest from researchers and has some potential prospects for application in both cognitive enhancement and therapeutic application. The distinct stages of adult neurogenesis, offer precise points for possible modulation by endogenous and exogenous factors if well understood. Nevertheless, there are some gaps that need to be addressed. Among them is the extent of adult neurogenesis from pre-adolescence to late adulthood. This is important as it will help to answer if new neurons generated would have a functional impact in humans.

Author contributions: *AOI conceptualized the research and the review of the topic, reviewed the manuscript and cleared for submission. LHT undertook literature search and prepared the draft of the manuscript under supervision of AOI. CD reviewed the manuscript.*
Conflicts of interest: *The authors declare no conflict of interest.*

References

Abdallah BNM, Slomianka L, Vyssotski AL, Lipp HP (2010) Early changes in adult hippocampal neurogenesis in C57 mice. Neurobiol Aging 31:151-161.

Ahmed AI, Zaben M, Gray WP (2011) Stem cells in the adult human brain. Br J Neurosurg 25:28-37.

Aimone JB, Deng W, Gage FH (2010) Adult neurogenesis: integrating theories and separating functions. Trends Cogn Sci 14:325-337.

Aizawa K, Ageyama N, Yokoyama C, Hisatsune T (2009) Age-dependent alteration in hippocampal neurogenesis correlates with learning performance ofmacaquemonkeys. Exp Anim 58:403-407.

Ajao MS, Olaleye O, Ihunwo AO (2010) Melatonin potentiates cells proliferation in the dentate gyrus following ischemic brain injury in adult rats. J Anim Vet Adv 9:1633-1638.

Allen E (1912) The cessation of the mitosis in the central nervous system of the albino rat. J Comp Neurol 22:547-568.

Altman J, Das GD (1965) Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 124.

Amaral DG, Witter MP (1989) The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 31:571-579.

Amrein I, Slomianka L, Lipp HP (2004a) Granule cell number, cell death and cell proliferation in the dentate gyrus of wild-living rodents. Eur J Neurosci 20:3342-3350.

Amrein I, Boonstra R, Lipp HP, Wojtowicz JM (2008) Adult hippocampal neurogenesis in natural populations of mammals. In: Adult Neurogenesis (Gage FH, Kempermann G, Song H, eds), pp 645-659. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press.

Amrein I, Slomianka L, Poletaeva I, Bologova NV, Lipp HP (2004b) 'Marked species and age-dependent differences in cell proliferation and neurogenesis in the hippocampus of wild-living rodents'. Hippocampus 14:1000-1010.

Andersson A (2010) Studies of neurogenesis in the adult human brain. In: Institutionen för Livsvetenskapliga studier Magisteruppsats 30 hp Södertörns University.

Balu DT, Lucki I (2009) Adult hippocampal neurogenesis: regulation, functional implications, and contribution to disease pathology. Neurosci Biobehav Rev 33:232-252.

Berg DA, Yoon KJ, Will B, Xiao AY, Kim N-S, Christian KM, Song H, Ming Gl (2015) Tbr2-expressing intermediate progenitor cells in the adult mouse hippocampus are unipotent neuronal precursors with limited amplification capacity under homeostasis. Front Biol 10:262-271.

Bergami M, Masserdotti G, Temprana Silvio G, Motori E, Eriksson Therese M, Göbel J, Yang Sung M, Conzelmann KK, Schinder Alejandro F, Götz M, Berninger B (2015) A Critical period for experience-dependent remodeling of adult-born neuron connectivity. Neuron 85:710-717.

Bertaina-Anglade V, Tramu G, Destrade C (2000) Differential learning-stage dependent patterns of c-Fos protein expression in brain regions during the acquisition and memory consolidation of an operant task in mice. Eur J Neurosci 12:3803-3812.

Biebl M, Cooper CM, Winkler J, Kuhn HG (2000) Analysis of neurogenesis and programmed cell death reveals a self-renewing capacity in the adult rat brain. Neurosci Lett 291:17-20.

Bofanti L (2016) Adult neurogenesis 50 years later: limits and opportunities in mammals. Front Nuerosci 10:44.

Bonfanti L, Peretto P (2007) Radial glial origin of the adult neural stem cells in the subventricular zone. Prog Neurobiol 83:24-36.

Bontempi B, Laurent-Demir C, Destrade C, Jaffard R (1999) Time-dependent reorganization of brain circuitry underlying long-term memory storage. Nature 400:671-675.

Bowers M, Jessberger S (2016) Linking adult hippocampal neurogenesis with human physiology and disease. Dev Dyn 245:702-709.

Brandt MD (2003) Transient calretinin expression defines early postmitotic step of neuronal differentiation in adult hippocampal neurogenesis of mice. Mol Cell Neurosci 24:603-613.

Braun SMG, Jessberger S (2014) Adult neurogenesis: mechanisms and functional significance. Development 141:1983-1986.

Bruel-Jungerman E, Rampon C, Laroche S (2007) Adult hippocampal neurogenesis, synaptic plasticity and memory: facts and hypotheses. Rev Neurosci 18:93-114.

Chawana R, Patzke N, Kaswera C, Gilissen E, Ihunwo AO, Manger PR (2013) Adult neurogenesis in eight Megachiropteran species. Neuroscience 244:159-172.

Couillard-Despres S, Vreys R, Aigner L, Van der Linden A (2011) In vivo monitoring of adult neurogenesis in health and disease. Front Neurosci 5:67.

Curtis MA, Kam M, Faull RL (2011) Neurogenesis in humans. Eur J Neurosci 33:1170-1174.

Czeh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, vanKampen M (2001) Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci U S A 98:12796-12801.

D'Alessio L, Konopka H, López EM, Seoane E, Consalvo D, Oddo S, Kochen S, López-Costa JJ (2010) Ddoublecortin (DCX) immunohistoreactivity in hippocampus of chronic reflectory temporal lobe epilepsy patients with hippocampal sclerosis. Seizure 19: 567-572.

Dayer AG, Ford AA, Cleaver KM, Yassaee M, Cameron HA (2003) Short-term and long-term survival of new neurons in the rat dentate gyrus. J Comp Neurol 460:563-572.

Del Bigio MR (1999) Proliferative status of cells in adult human dentate gyrus. Microsc Res Tech 45:6.

Dennis CV, Suh LS, Rodriguez ML, Kril JJ, Sutherland GT (2016) Human adult neurogenesis across the ages: Animmunohistochemical study. Neuropathol Appl Neurobiol doi:10.1111/nan.12337.

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A (1999) Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell 97:703-716.

Duan X, Chang JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y, Liu XB, Yang CH, Jordan JD, Ma DK, Liu CY, Ganesan S, Cheng HJ, Ming Gl, Lu B, Song H (2007) Disrupted-in-schizophrenia 1 regulates integration of newly generated neurons in the adult brain. Cell 130:1146-1158.

Erickson CA, Barnes CA (2003) The neurobiology of memory changes in normal aging. Exp Gerontol 38:61-69.
Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA (1998) Neurogenesis in the adult human hippocampus. Nat Med 4:1313-1317.
Esposito MS (2005) Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J Neurosci 25:10074-10086.
Fahrner A, Kann G, Flubacher A, Heinrich C, Freiman TM, Zentner J, Frotscher M, Haas CA (2007) Granule cell dispersion is not accompanied by enhanced neurogenesis in temporal lobe epilepsy patients. Exp Neurol 203:320-332.
Friedman SD (2008) Comment on "Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain". Science 321:640.
Göritz C, Frisén J (2012) Neural stem cells and neurogenesis in the adult. Cell Stem Cell 10:657-659.
Gage FH (2000) Mammalian neural stem cells. Science 287: 1433-1438.
Gage FH (2002) Neurogenesis in the adult brain. J Neurosci 22:612-613.
Gage FH, van Praag H (2002) Neurogenesis in adult brain. Neuropsychopharmacology 27:109-117.
Ge S (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 439:589-593.
Georg Kuhn H, Blomgren K (2011) Developmental dysregulation of adult neurogenesis. Eur J Neurosci 33:1115-1122.
Gould E, Gross CG (2002) Neurogenesis in adult mammals: some progress and problems. J Neurosci 22:619-623.
Gould E, Cameron HA, McEwen BS (1994) Blockade of NMDA receptors increases cell death and birth in the developing rat dentate gyrus. J Comp Neurol 340:551-565.
Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E (1998) Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A 95:3168-3171.
Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E (1999) Hippocampal neurogenesis in adult Old World primates. Proc Natl Acad Sci U S A 96:5263-5267.
Gross CG (2000) Neurogenesis in the adult brain: death of a dogma. Nat Rev Neurosci 1:67-73.
Gu Y, Janoschka S, Ge S (2013) Neurogenesis and Hippocampal Plasticity in Adult Brain. In: Neurogenesis and Neural Plasticity (Belzung C, Wigmore P, eds), pp 31-48. Berlin, Heidelberg: Springer Berlin Heidelberg.
Gu Y, Arruda-Carvalho M, Wang J, Janoschka S, Josselyn S, Frankland P, Ge S (2012) Optical controlling reveals time-dependent roles for adult-born dentate granule cells. Nat Neurosci 15:1700-1706.
Hastings NB, Gould E (1999) Rapid extension of axons into the CA3 region by adult-generated granule cells. J Comp Neurol 413:146-154.
Hayashi ML, Choi SY, Rao BS, Jung HY, Lee HK, Zhang D, Chattarji S, Kirkwood A, Tonegawa S (2004) Altered cortical synaptic morphology and impaired memory consolidation in forebrain- specific dominant-negative PAK transgenic mice. Neuron 42:773-787.
Hong CJ, Park H, Yu S (2016) Autophagy for the quality control of adult hippocampal neural stem cells. Brain Res 1649:166-172.
Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, Yamaguchi M, Mori K, Ikeda T, Itohara S, Kageyama R (2008) Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat Neurosci 11:1153-1161.
Jansen JFA, Gearhart JD, Bulte JWM (2008) Comment on"Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. Science 321:640.
Jessberger S, Kempermann G (2003) Adult-born hippocampal neurons mature into activity-dependent responsiveness. Eur J Neurosci 18:2707-2712.
Jessberger S, Gage FH (2014) Adult neurogenesis: bridging the gap between mice and humans. Trend Cell Biol 24:558-563.
Jin K, Peel AL, Mao XO, Xie L, Cottrell BA, Henshall DC, Greenberg DA (2004a) Increased hippocampal neurogenesis in Alzheimer's disease. Proc Natl Acad Sci U S A 101:343-347.
Jin K, Galvan V, Xie L, Mao XO, Gorostiza OF, Bredesen DE, Greenberg DA (2004b) Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPSw,Ind) mice. Proc Natl Acad Sci U S A 101:13363-13367.
Kee N, Teixeira CM, Wang AH, Frankland PW (2007) Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. Nat Neurosci 10:355-362.
Kempermann G, Gast D, Kronenberg G, Yamaguchi M, Gage FH (2003) Early determination and long-term persistence of adult-generated new neurons in the hippocampus of mice. Development 130:391-399.
Kitamura T, Sugiyama H (2006) Running wheel exercises accelerate neuronal turnover in mouse dentate gyrus. Neurosci Res 56:45-52.
Kitamura T, Inokuchi K (2014) Role of adult neurogenesis in hippocampal-cortical memory consolidation. Mol Brain 7:1-8.
Knobloch M, Jesseberger S (2011) Editorial: Perspectives on adult neurogenesis. Eur J Neurosci 33:1013-1017.
Kobayashi K, Poo MM (2004) Spike train timing-dependent associative modification of hippocampal CA3 recurrent synapses by mossy fibers. Neuron 41:445-454.
Korbo L, Amrein L, Lipp HP, Wolfer D, Regeur L, Oster S, Pakkenberg B (2004) No evidence for loss of hippocampal neurons in non-Alzheimer dementia patients. Acta Neurol Scand 109:132-139.
Kornack DR, Rakic P (1999) Continuation of neurogenesis in the hippocampus of the adult macaque monkey. Proc Natl Acad Sci U S A 96:5768-5773.
Kuhn HG, Dickinson-Anson H, Gage FH (1996) Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 16:2027-2033.
Lafenetre P, Leske O, Wahle P, Heumann R (2011) The beneficial effect of physical activity on impaired adult neurogenesis and cognitive performance. Front Neurosci 5:Article 51.
Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, van Praag H (2010) When neurogenesis encounters aging and disease. Trend Neurosci 33:569-579.
Liu YW, Curtis MA, Gibbons HM, Mee EW, Bergin PS, Teoh HH, Connor B, Dragunow M, Faull RL (2008) Doublecortin expression in the normal and epileptic adult human brain. Neurosystems 28 2254-2265.
Loi M, Koricka S, Lucassen P, Joels M (2014) Age- and sex-dependent effects of early life stress on hippocampal neurogenesis. Front Endocrinol 5:13.
Lois C, Alvarez-Buylla A (1993) Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. Proc Natl Acad Sci U S A 90:2074-2077.
Luu P, Sill OC, Gao L, Becker S, Wojtowicz JM, Smith DM (2012) The role of adult hippocampal neurogenesis in reducing interference. Behav Neurosci 126:381-391.
Manganas LN, Zhang X, Li, Y., Hazel RD, Smith SD, Wagshul ME, Henn F, Benveniste H, Djuric PM, Enikolopov G, Maletic-Savatic M (2007) Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. Science 318:980-985.
Marin-Burgin A, Schinder AF (2012) Requirement of adult-born neurons for hippocampus-dependent learning. Behav Brain Res 227:391-399.
Marques AA, Bevilaqua MCN, da Fonseca AMP, Nardi AE, Thuret S, Dias GP (2016) Gender differences in neurobilogy of anxiety: focus on adult neurogenesis. Neural Plast 2016:5026713.
Merkle FT, Mirzadeh Z, Alvarez-Buylla A (2007) Mosaic organisation of neural stem cells in the adult brain. Science 317:381-384.
Ming GL, Song H (2005) Adult neurogenesis in the mammalian central nervous system. Annu Rev Neurosci 28:223-250.
Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neurosciences 70:687-702.
Muddanna S Rao, Bharathi Hattiangady, Ashok K. Shetty (2008) Status epilepticus during old age is not associated with enhanced hippocampal neurogenesis. Hippocampus 18:931-944.
Naruse I, Keino H (1995) Apoptosis in the developing CNS. Prog Neurobiol 47:135-155.
Ngwenya LB, Heyworth NC, Shwe Y, Moore T, Rosene DL (2015) Age-related changes in dentate gyrus cell numbers, neurogenesis, and associations with cognitive impairements in the rhesus monkey. Front Syst Neurosci 9:102.

Nogueira AB, Sogayar MC, Colquhoun A, Siqueira SA, Nogueira AB, Marchiori PE, Teixeira MJ (2014) Existence of a potential neurogenic system in the adult human brain. J Transl Med 12:75.
Nottebohm F (1985) Neuronal replacement in adulthood. Ann N Y Acad Sci 457:143-161.
Nottebohm F (1989) A brain for all seasons: cyclical anatomical changes in song control nuclei of the adult female canary brain. Science 214:1368-1370.
Olude A, Olopade J, Ihunwo A (2014) Adult neurogenesis in the African giant rat (Cricetomysgambianus, waterhouse). Metab Brain Dis 29: 857-866.
Oppenheim RW (1991) Cell death during development of the nervous system. Annu Rev Neurosci 14:453-501.
Palmer TD, Schwartz PH, Taupin P, Kaspar BK, Stein SA, Gage FH (2001) Cell culture. Progenitor cells from human brain after death. Nature 411:42-43.
Patzke N, Spocter MA, Karlsson KA, Bertelsen MF, Haagensen M, Chawana R, Streicher S, Kaswera C, Gilissen E, Alagaili AN, Mohammed OB, Reep RL, Bennett NC, Siegel JM, Ihunwo AO, Manger PR (2015) In contrast to many other mammals, cetaceans have relatively small hippocampi that appear to lack adult neurogenesis. Brain Struct Funct 220:361-383.
Perotin SG, Alvarez-Buylla A, Garcia-Verdugo J (2009) Identification and characterisation of neural progenitor cells in the adult mammalian brain. Verlag Berlin Heidelberg: Springer.
Ramon y Cajal S (1928) Degeneration and regeneration of the nervous system. New York: Hafner.
Rao MS, Hattiangady B, Shetty AK (2008) Status epilepticus during old age is not associated with enhanced hippocampal neurogenesis. Hippocampus 18:931-944.
Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch KP (2006) Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 11:514-522.
Robinson TE, Kolb B (1997) Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. J Neurosci 17:8491-8497.
Rotheneichner P, Marschallinger J, Couillard-Despres S, Aigner L (2013) Neurogenesis and neuronal regeneration in status epilepticus. Epilepsia 54 Suppl 6:40-42.
Sahay A, Scobie KN, Hill AS, O'Carroll CM, Kheirbek MA, Burghardt NS, Fenton AA, Dranovsky A, Hen R (2011) Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472:466-470.
Satvat E, Schmidt B, Argraves M, Marrone DF, Markus EJ (2011) Changes in task demands alter the pattern of zif268 expression in the dentate gyrus. J Neurosci 31:7163-7167.
Schmidt-Hieber C, Jonas P, Bischofberger J (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429:184-187.
Seress L, Abraham H, Tornoczky T, Kasztolanyi G (2001) Cell formation in the human hippocampal formation from mid-gestation to late postnatal period. Neuroscience 105:831-843.
Sierra A, Encianas J, Maletic-Savatic (2011) Adult human neurogenesis: from microscopy to magnetic resonance imaging. Front Nuerosci 5:1-18.
Snyder JS, Cameron HA (2012) Could adult hippocampal neurogenesis be relevant for human behavior? Behav Brain Res 227:384-390.
Song H (2005) New neurons in the adult mammalian brain: synaptogenesis and functional integration. J Neurosci 25:10366-10368.
Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, Bostrom E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisén J (2013) Dynamics of hippocampal neurogenesis in adult humans. Cell 153:1219-1227.
Stanfield BB, Trice JE (1988) Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. Exp Brain Res 72:399-406.
Starkman MN, Giordani B, Gebarski SS, Berent S, Schork MA, Schteingart DE (1999) Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. Biol Psychiatry 46:1595-1602.
Suhonen JO, Peterson DA, Ray J, Gage FH (1996) Differentiation of adult hippocampus-derived progenitors into olfactory neurons in vivo. Nature 383:624-627.
Sun W (2004) Programmed cell death of adult-generated hippocampal neurons is mediated by the proapoptotic gene Bax. J Neurosci 24:11205-11213.
Tashiro A, Makino H, Gage FH (2007) Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci 27:3252-3259.
Tashiro A, Sandler VM, Toni N, Zhao C, Gage FH (2006) NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. Nature 442:929-933.
Thom M, Martinian L, Williams G, Stoeber K, Sisodiya SM (2005) Cell proliferation and granule cell dispersion in human hippocampus sclerosis. J Neuropathol Exp Neurol 64:194-201.
Thompson A, Boekhoorn K, Van Dam AM, Lucassen PJ (2008) Changes in adult neurogenesis in neurodegenerative diseases: cause or consequence? Genes Brain Behav 7:28-42.
Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, Gage FH, Schinder AF (2008) Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci 11:901-907.
van Praag H (2002) Functional neurogenesis in the adult hippocampus. Nature 415:1030-1034.
Wiskott L, Rasch MJ, Kempermann G (2006) A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus. Hippocampus 16:329-343.
Yuan J, Yankner BA (2000) Apoptosis in the nervous system. Nature 407:802-809.
Zhang CL, Zou Y, He W, Gage FH, Evans RM (2008) A role for adult TLX-positive neural stem cells in learning and behaviour. Nature 451.
Zhao C, Deng W, Gage FH (2008) Mechanisms and functional implications of adult neurogenesis. Cell 132:645-660.
Zhao C, Teng EM, Summers RG, Ming GL, Gage FH (2006) Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci 26:3-11.
Zupanc GH (1999) Neurogenesis, cell death and regeneration in the adult Gymnotiform brain. J Exp Biol 202:1435-1446.