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Cell-based therapies for disorders of the CNS

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There are few effective pharmacological-based treatments for acute neurological trauma or chronic neurodegenerative diseases. This has created a demand for innovative therapeutic approaches including gene therapy, deep brain stimulation and cell-based therapies. This review, briefly updates the progress made in recent clinical trials of neurotransplantation in Parkinson's and Huntington's disease, discusses challenges that still have to be overcome, and reviews the progress in meeting these challenges. The main focus of this review, however, will be on recent advances in using endogenous neural precursor cells (NPCs) to promote brain repair. The physiological role of NPCs, their response to various types of injury and other endogenous and exogenous factors will be discussed. Finally, their therapeutic potential and relevance to human disease will be considered.

Keywords: cell therapy, neural precursor cell, neurotransplantation, stem cell

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1. Introduction

Neurological disorders place a large burden on medical resources in many countries and have serious consequences for affected individuals and their families. These conditions include stroke, physical trauma and neurodegenerative diseases, such as Alzheimer's (AD), Parkinson's (PD), and Huntington's disease (HD). Treatments for these conditions are few, target mainly the symptoms, and do little to address the primary causes. In addition, such therapies rarely affect the onset or progression of the disease, or modify the underlying pathology in any substantial way. Therefore, more curative therapeutic approaches are being considered, such as gene therapy, deep brain stimulation, and the use of neurotrophic factors and cell transplantation, which to date has mainly concentrated on the transplanting of fetal-derived cells into the degenerating adult brain. However, recently a different approach has been considered that has yet to be tested clinically and which consists of stimulating the resident neural precursor cells in the adult brain to proliferate, migrate and differentiate into the appropriate cell type, thereby replacing cells that have been lost through trauma or degeneration.

In order to discuss such topics, to what extent cell-based treatments have been effective and what the realistic expectations of these approaches are has to be considered. In a previous paper in this journal we discussed stem cell transplantation as a therapeutic approach for brain repair [1]. Here, the clinical progress made in neurotransplantation together with recent advances in stem cell technology are updated, and the future prospects for this area of reparative neurobiology are briefly discussed. In particular, the interest and possibility of cell replacement by stimulation of endogenous neural precursor cells has grown in recent years and therefore the physiological role of NPCs, their response to injury, their ability to be manipulated *in vivo*, and their therapeutic potential will be discussed in greater detail.

2. Cell-based therapeutic approaches

In various neurological conditions, cells are lost either through an acute insult (e.g., stroke or physical trauma) or through a chronic degenerative process (e.g., PD). The rationale behind cell-based approaches is to replace these lost cells either by transplanting cells directly into the brain, or by stimulating endogenous neural precursor cells to divide and replenish cell populations.

2.1 Transplantation

There are three approaches using neurotransplantation that have been employed for the treatment of neurological disorders. The first is a replacement strategy that seeks to replace cells of a specific type in the area or areas in which they are lost pathologically, and thereby reconstruct neural circuitry. The second approach is a molecular one, which seeks not to replace cells *per se*, but to replace a neurochemical that has been diminished due to cell loss. The third approach is not simply to replace a lost neurochemical, but to introduce new therapeutic molecules into the brain that promote innate plasticity and repair, and which typically involves engineering cells to produce the molecule of interest (e.g., a neurotrophic factor). Each of these approaches is discussed in detail below.

2.1.1 Cell replacement designed to restore neural circuits

HD is a hereditary, progressive, degenerative disorder caused by an expanded CAG repeat in the *huntingtin* gene and is part of a family of disorders that have expanded polyglutamine tracts as their hallmark genetic feature. HD is characterised clinically by abnormal movements (typically chorea), with cognitive and psychiatric disturbances being common accompaniments. Neuropathologically, the early stages of disease are characterised by a substantial loss of GABAergic medium spiny neurons (MSN) in the striatum, although, even in early to mid stages of the disease, widespread pathology can be observed in many other brain regions [2]. Nevertheless, MSNs, which send projections to the globus pallidus, take the brunt of the early pathology and it is the loss of this striatal-pallidal circuit that, in part, accounts for the early motor and cognitive abnormalities in HD. Thus, in this disease, the aim of cell replacement therapy is to transplant cells into the striatum to replace MSNs and, by doing so, reconstruct the circuitry between the striatum and globus pallidus. This requires that transplanted cells mature appropriately, receive appropriate synaptic connections from host afferent axons, as well as send projections to target structures with the formation of normal connections.

Over the last 20 years, studies in animal models of HD have demonstrated that such circuit reconstruction with functional benefits is possible using fetal striatal allografts [3] and as a result clinical trials began in the mid-1990s. To date, however, there have overall been relatively few such trials adopting this approach in HD, especially when compared to neural transplantation in PD (discussed below). Furthermore, all studies using human fetal striatal allografts in HD have been open-label, and so it is difficult to draw any firm conclusions on the efficacy of this approach. Nevertheless, one group in France has shown some efficacy using this strategy [4,5], although in this study, the rate of progression of the disease prior to transplantation was different in the transplanted patients compared to the controls, making interpretation of the results difficult [6].

Other candidate diseases for cell replacement therapy with the aim of circuit reconstruction, and that have now advanced to the stage of clinical trials, include stroke [7] and amyotropic lateral sclerosis [8], but the data to date is limited and so will not be discussed further in this review.

2.1.2 Molecular replacement designed to restore missing neurochemicals to normal

In PD, the cells that predominately degenerate are the dopamine-producing neurons with their cell bodies located in the substantia nigra pars compacta (SNpc). These cells send the majority of their axons to the striatum, but also have projections to other structures, such as the olfactory bulb, medial olfactory nuclei, amygdala, hippocampus, subthalamic nucleus, locus coeruleus and pyriform cortex [9]. It is the degeneration of the nigrostriatal pathway that is believed to cause many of the motor symptoms of PD, and so current pharmacological therapies targeted on this pathway are effective treatments for these clinical features.

As a consequence, the strategy for neurotransplantation in PD has been to implant dopamine-producing cells into the striatum where they can restore dopamine levels back to normal. However, in PD there are changes in other dopamine systems within the brain, together with pathology in structures other than the SNpc [10], which will always mean that there are limits to the therapeutic efficacy of transplanting dopaminergic cells only into the striatum.

This having been said, however, transplantation in animal models of PD have demonstrated the safety and efficacy of this approach using fetal nigral allografts and, as such, has lead to numerous clinical trials [11]. A recent meta-analysis of 11 of these studies (10 of which were open-label) with a total of 95 patients has shown an improvement in a number of clinical outcomes [12]. There have also been two double-blind placebo-controlled trials that have been somewhat disappointing in their results. In the first study, there was no significant difference in the primary outcome measure, which was the patients' subjective rating of their improvement one year post-transplantation [13,14]. In addition 15% of patients developed dyskinesias off medication, which led in a few cases to further surgical intervention because of their severity [15]. It should be noted, however, that there were significant methodological differences between this study and previous open-label studies, which makes comparisons of efficacy difficult [16]. In the second study, there was also no significant improvement in the primary outcome – the Unified PD Rating Scale

(UPDRS) motor score at 24 months after transplantation, and some patients in this study also developed dyskinesias [17] (see [11] for a more detailed discussion). This problem with dyskinesias post-transplantation has been a serious unexpected complication and as such, numerous groups are now focusing on the reasons underlying the development of these abnormal movements.

However, it should be realised that the results of some patients who have undergone such procedures have been dramatic [18], and the main challenge of dopamine replacement in the striatum in PD is consistency of outcome, which may relate as much to patient selection as to the transplantation itself.

2.1.3 Ex vivo *gene therapy and delivery of therapeutic agents to promote innate repair*

In addition to transplanting cells to reconstruct neural circuits or to replace neurochemicals, transplanting cells that have been modified to produce a therapeutic molecule represent a third strategy. This approach presents the same challenges and risks as above, and in addition, there is the concern that genetically modified cells may be more prone to form tumours if the transfected gene inserts into an inappropriate place (insertional mutagenesis) and either disrupts the expression of a tumour-suppressor gene or activates an oncogene [19].

This approach has recently been adopted in a Phase I clinical trial for HD, in which a human cell line engineered to produce ciliary neurotrophic factor (CNTF) was encapsulated in a semipermeable membrane, and transplanted into the right lateral ventricle of six patients with mild-to-moderate HD [20]. This was based on a similar approach showing efficacy in a primate model of HD [21]. Capsules were retrieved every six months and replaced with new ones. There was no significant clinical improvement in any of the six subjects on neurological, neuropsychological or motor tests. There was some improvement in electrophysiological results, but there was a variable amount of surviving cells in the retrieved capsules and CNTF release was low in 13/28 capsules.

2.1.4 Drawbacks and challenges with these three approaches

Whilst these approaches with human fetal tissue may one day prove consistently effective, there are a number of issues that will always exist and additional issues that need to be resolved (**Box 1**). First, as with any surgery, there is the risk of complication or infection, either from the surgery itself or by the use of contaminated tissue, and this includes the possibility of prion disease. However, if these approaches eventually become effective and reproducible, the considerable benefits to be gained would likely outweigh any such surgical risks. A second major difficulty at present is obtaining sufficient quantities of cells to transplant into patients and this in itself has been a major catalyst into research involving other cell sources, especially stem cells. A third and related problem is the ethical issues surrounding the use of aborted human fetuses and embryonic stem (ES) cells. Fourth, procedures for collecting, dissecting, storing and transplanting cells are not standardised and have varied between studies, therefore making comparisons difficult. In addition to standardisation there is still scope to improve and optimise the above procedures and only when this has been done can proper double-blind placebo-controlled trials be considered. As mentioned above, a fifth concern relating to the use of cell lines or some form of stem cell is the possibility of the transplanted cells forming tumours, especially if the cells have also been subject to genetic manipulation. Sixth, the development of dyskinesias with PD in two recent studies has demonstrated that cell transplantation may have unintended side effects, which, if they cannot be mitigated, make the technique less attractive. This may have its origins as much in patient selection as with the method of transplantation itself. A seventh and related point is that transplanting cells is a permanent procedure and if tumours form or dyskinesias develop, it is not possible to discontinue treatment as it would be for deep brain stimulation or a pharmaceutical-based approach. Eighth, present strategies produce variable results, which is not unexpected given that procedures differ between studies and even within studies as procedural issues are improved with experience.

For transplantation-based approaches to become more widespread the results must become much more reproducible, which will require using a homogeneous population of cells with standardised transplantation procedures in appropriate patients. A final point to consider is that the efficacy of any transplantation therapy has to be compared to the results that can be obtained by current pharmacological or neurosurgical treatments, such as L-Dopa therapy or deep brain stimulation in PD. Only if it shows a long-term advantage can it be considered a successful therapy to use.

Box 1. Drawbacks and challenges of cell transplantation into the brain.

- Need better patient selection… but then fewer people are eligible
- Source(s) of cells often limited in quality and quantity
- Ethical issues involving the use of human fetuses or embryos and cells derived from them
- Procedures not standardised or optimised
- Treatment not reversible
- Surgical complications and risk of infection, including prion disease
- Need for immunosuppression and subsequent risks that this causes
- Possibility of tumour formation
- Possibility of dyskinesias developing
- Efficacy is not better than current treatments

2.1.5 Response to challenges by the biotechnology industry

The need for a large number of suitable cells is one of the major obstacles that this approach has to overcome, and this need is also receiving attention from a number of biotechnology companies. Instead of continuing to use primary grafts of human fetuses, it is anticipated that stem cells derived from various sources might provide more readily available cells for neurotransplantation [1]. Whilst ES cells derived from the inner cell mass of embryos can form multiple cell types, there are ethical as well as practical concerns about the use of such cells, including the ability to patent cells derived from such a source. Multipotent cells can be derived from other sources, however, including the umbilical cord [22] and bone marrow [23]. Using haematopoietic stem cells derived from umbilical cord blood, Anthrogenesis Corp. has claimed a method of differentiating these cells into neuronal phenotypes using a variety of growth factors, cytokines, hormones and elements from the extracellular matrix (e.g., collagen, laminin etc.) for the treatment of various neurological conditions [201]. Parmicell Ltd has invented a method of differentiating and proliferating mesenchymal stem cells into neural cells by culturing mesenchymal cells in a medium containing epidermal growth factor and hepatocyte growth factor [202].

In addition to deriving cells from novel sources, the ability to differentiate cells into the appropriate phenotype is of great importance. Axordia Ltd has developed a method to promote the differentiation of stem cells using RNA interference, by the introduction of stem-loop RNA into the cell comprising a sequence of a gene that mediates at least one step in the differentiation of the cell, and/or maintaining the cell in a differentiated state [203]. Typically, the stem-loop RNA will be directed towards the mRNA products of genes that are involved with cellular differentiation, including those encoding cell surface receptors, ligands or transcription factors.

Whilst progress is being made towards finding better cells for transplantation, another cell-based approach has been receiving interest in the past few years. This newer approach avoids many of the drawbacks of transplanting cells into the brain and involves endogenous neural precursor cells.

2.2 Endogenous neural precursor cells

One of the most notable advances in neuroscience in the past 15 years is the discovery that adult mammals continue to produce new neurons in certain regions of the brain. Previously, it was believed that mammals were born with all the neurons that they would possess and that the number of neurons progressively declined during the life of the organism. This dogma has been overturned as it has been definitively demonstrated that in a few selective regions of the brain, including the human brain, there are resident populations of cells that continue to generate new neurons from endogenous neural precursor cells throughout adulthood – a process referred to as adult neurogenesis. These new neurons functionally integrate into the existing neuronal circuitry and are related to behavioural outcomes; in particular learning and memory.

In the adult mammal, neurogenesis has been characterised primarily in the olfactory bulb, arising after migration from progenitor cells located in the subventricular zone (SVZ) lining the lateral ventricular wall, and in the subgranular zone (SGZ) of the hippocampal dentate gyrus (**Figure 1**), with the first report occurring in the 1960s [24]. Proliferation of these cells can be detected using ^{3}H-thymidine or bromodeoxyuridine (BrdU), which are nucleotide analogues that can be injected into living animals (or can be administered in the drinking water), and label dividing cells by incorporation into replicating DNA. ^{3}H-thymidine can be detected *in situ* by autoradiography and BrdU, which has become the more commonly used method, by immunohistochemistry [25]. Whilst there have been reports of neurogenesis in other areas of the adult brain, such as the neocortex [26] and substantia nigra [27], these findings have been criticised on methodological grounds [28] and have failed to be replicated by others [29-31]. Other studies have demonstrated neurogenesis in the dorsal vagal complex of the brain stem [32], amygdala, piriform cortex and inferior temporal cortex [33], although these studies are awaiting replication. In addition, it does appear that cortical neurogenesis can be appropriately induced under certain conditions, such as the use of a lesion that selectively kills cortical neurons through induction of programmed cell death [34]; whether this occurs under normal physiological or pathological conditions remains to be determined.

Whilst neurogenesis is often referred to as a single process, there are four distinct events that determine the number of new neurons formed:

- Proliferation, or simply the rate at which neural precursor cells divide.
- Migration, which refers to the final destination of these cells. For example, progenies of the rodent SVZ stem cells travel along the rostral migratory stream and end up in the olfactory bulb.
- Differentiation, defines the fate of these cells as they mature into specific neural phenotypes, namely neurons, astrocytes or oligodendrocytes. The proportion of each cell type may vary under different physiological or experimental conditions.
- Survival of these cells, which over time ultimately affects the total cell number, as many newly divided cells do not survive for a long period of time [35].

It is a combination of all four of these factors that will determine the net cell increase (or decrease) of neurons.

These proliferative cells, referred to as neural precursor cells in this paper, have been further characterised to a lineage based on immunocytochemical and morphological criteria. In the SVZ these cells have been divided into neural stem cells (also known as B cells), which give rise to transit amplifying cells (C cells), and which then become migrating neuroblasts (A cells) that travel along the rostral migratory

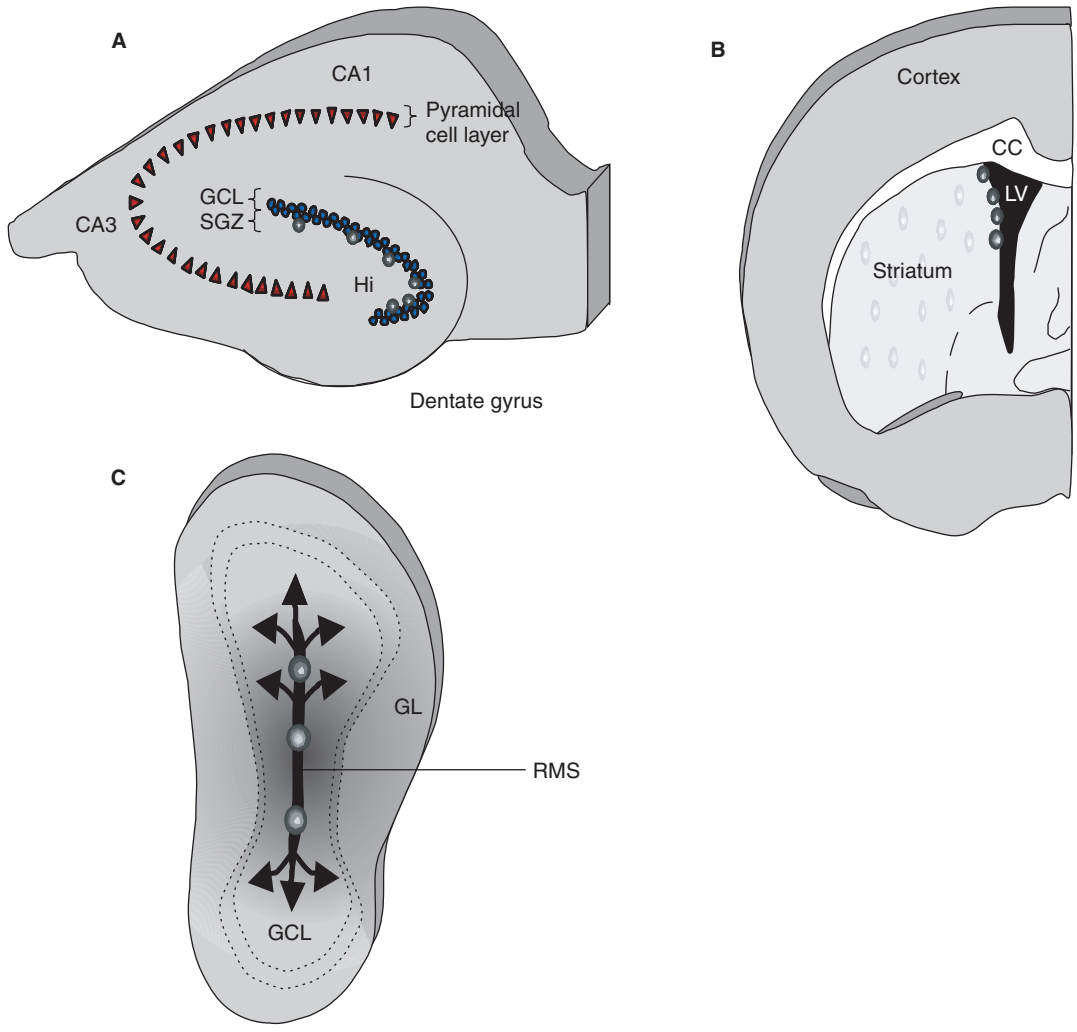

Figure 1. Neurogenesis in the rodent brain. A) Hippocampal neurogenesis occurs in the subgranular zone on the concave side of the granule cell layer in the dentate gyrus; **B**) Proliferation of neural precursor cells occurs in the subventricular zone beside the lateral ventricles; **C**) Some of these cells migrate along the rostral migratory stream to the olfactory bulb where they then migrate radially (arrows) and differentiate into neurons.
CC: Corpus callosum; GCL: Granule cell layer; GL: Glomerular layer; Hi: Hilus; LV: Lateral ventricle; RMS: Rostral migratory stream; SGZ: Subgranular zone.

stream into the olfactory bulb [36]. In the SGZ of the dentate gyrus, proliferative cells have been characterised into stem cells, transiently amplifying cells, immature neurons and mature neurons [37].

Neurogenesis also appears to occur in a special microenvironment, or 'neurogenic niche', where proliferative cells are found around small capillaries in tight clusters with committed neuroblasts, glia and endothelial cell precursors [38]. In addition to the close physical proximity between NPCs and capillary endothelial cells, both are responsive to similar factors. This includes both angiogenic factors, such as vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF) and erythropoietin, which have effects on the nervous system; and neurogenic factors, such as brain derived neurotrophic factor (BDNF), glial derived neurotrophic factor (GDNF) and nerve growth factor (NGF), which have effects on the vascular system (reviewed in [39,40]). Furthermore, it is the endothelial cells that produce some of these factors (e.g., BDNF), which provide local cues for NPCs. This suggests that neurogenesis is regulated, in part, by the microenvironment of NPCs.

2.2.1 Physiological role of neural precursor cells

The physiological role for hippocampal neurogenesis is not completely understood, but it has been demonstrated that newly formed cells in the hippocampus form synaptic connections and become functionally integrated into the existing circuitry in rodents [41-43]. In addition, new cells have different electrophysiological properties than older neurons.

For example, in new neurons it is easier to induce long-term potentiation (LTP) [44,45], which is perhaps the best electrophysiological correlate of learning and, as such, it may be easier for these cells to respond to novel stimuli compared to existing older cells. Functional integration of new neurons in the olfactory bulb also occurs and the relevance of these new neurons in olfactory information processing has been recently reviewed [46,47].

To support such a role for NPCs, levels of neurogenesis have been correlated with learning and memory in a number of studies using a variety of approaches. Although there appears to be good evidence for a relationship between neurogenesis and certain types of cognitive performance, it should be noted that many of these results are correlational and therefore do not establish causality. Furthermore, many of these studies do not rule out the possibility that other changes occurring in the hippocampus may account for the results (e.g., changes in LTP). For example, it has been demonstrated that when neurogenesis is increased via physical exercise in mice (wheel running), performance on the Morris water maze improves [48]. It is known that wheel running increases LTP, which means that improvement on the water maze could be attributed to changes in synaptic transmission in established neural circuits as much as to any change in neurogenesis. Furthermore, in a follow-up study by this same group, changes were also observed in hippocampal mRNA levels of various genes in those rats that had access to a running wheel, further complicating the relationship between neurogenesis, synaptic changes and behaviour [49]. In addition, another study showed that mice reared in isolation have poorer performance on the Morris water maze, less proliferation of cells in the dentate gyrus, and reduced LTP compared with rats reared in groups [50]. Therefore, it is difficult to establish the extent to which performance on the water maze can be accounted for by changes in neurogenesis versus changes in LTP, as both factors appear to play a role.

Further support is derived from a series of studies by Kempermann and Gage who demonstrated that different strains of mice, which have different basal levels of neurogenesis, also have different cognitive abilities. For example, C57BL/6 mice had high levels of neurogenesis and good performance on the Morris water maze, whereas 129/SvJ mice had both low levels of neurogenesis and poor performance [51]. Similar results were obtained in a different study using ten different strains of mice [52] although, as the authors note, it is possible that there might be other differences in these strains outside differences in neurogenesis that account for differential performance on the water maze.

A causal role for adult neurogenesis was first demonstrated by decreasing neurogenesis in rats using an antimitotic agent, which decreased performance on a hippocampal-dependent memory task, but not on a hippocampal-independent task [53]. Furthermore, when the antimitotic treatment was stopped, performance on the hippocampal-dependent task recovered. Thus, because performance on the hippocampal-independent task remained unchanged and the hippocampal deficit was reversible, it is more likely that changes in performance in the hippocampal-dependent task were causally due to changes in neurogenesis.

Another study demonstrated how the natural variation in performance on the Morris water maze in a group of aged rats could predict which mice had higher or lower levels of neurogenesis. Aged mice that were cognitively unimpaired had higher levels of neurogenesis compared with their cognitively impaired littermates [54]. There is also evidence that hippocampal-dependent learning increases neurogenesis, whilst hippocampal-independent learning does not [55]. To summarise, higher levels of neurogenesis are associated with better performance on hippocampal-dependent tasks and tasks that require hippocampal action appear to increase neurogenesis. Although there is no direct evidence to suggest that too much neurogenesis may in fact be detrimental to learning, it has been proposed that the relationship between neurogenesis and behaviour might be an inverted 'U' shape, where there is an optimal amount of neurogenesis, and as one deviates from this in either direction performance on behavioural tasks deteriorates [56].

Taken together, these and other studies have demonstrated that a relationship exists between memory/learning and hippocampal neurogenesis with weaker and indirect evidence suggesting that neurogenesis might account for changes in cognitive function. However, it has yet to be determined to what extent neurogenesis plays a role in behavioural outcomes, as there are often other factors, such as changes in LTP and gene expression, that need to be accounted for in any model that relates neurogenesis to behaviour (**Figure 2**).

In addition to the relationship between neurogenesis and memory/learning, there appears to be a relationship between hippocampal neurogenesis and depression, with low levels of neurogenesis being associated with depression. There are five lines of evidence for this.

- A number of antidepressants increase neurogenesis in animal models [57], and in one study hippocampal neurogenesis was shown to be required for the effects of antidepressants [58].
- It is known that depression is associated with decreased levels of serotonin [59] and that serotonin depletion decreases neurogenesis, whilst serotonin replacement increases neurogenesis [60-62].
- Electroconvulsive therapy is a treatment for severe depression and also increases neurogenesis in an animal model [63].
- Exercise increases neurogenesis and has also been shown to improve symptoms of depression [64].
- If antidepressants work by increasing neurogenesis, this would explain why it often takes three to four weeks for the effects of antidepressants to be seen [65], as it takes this amount of time for new neurons to functionally integrate into the existing circuitry.

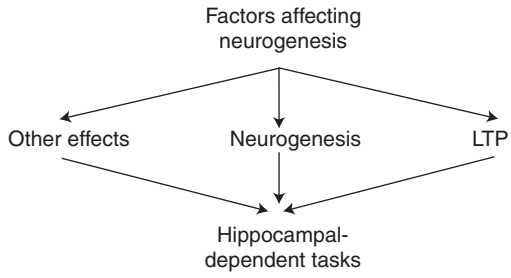

Figure 2. Various factors affect neurogenesis and changes in neurogenesis affects hippocampal-dependent behavioural tasks. Some factors, such as wheel running, also change LTP, which independent of changes in neurogenesis, influences performance on behavioural tasks. Further, there might be other effects such as changes in vascularisation in the brain or gene expression that might mediate changes in neurogenesis and/or directly affect performance on behavioural tasks.
LTP: Long-term potentiation.

Neurogenesis in the subventricular zone/olfactory bulb (OB) system also has an influence on behaviour, and under normal physiological conditions it appears to be primarily involved in olfactory learning and odour discrimination in rodents, and therefore may have less biological impact in humans [46]. Some of these newly divided cells located in the SVZ express the polysialylated form of neural cell adhesion molecule (PSA-NCAM) and migrate to the OB where they form granule neurons and periglomerular interneurons [66]. PSA-NCAM is involved with the characteristic chain migration observed in these cells [67] and NCAM double-knockout mice have smaller OBs, a larger numbers of cells in the rostral migratory stream (indicating lack of migration to the OB) and are not as good at odour discrimination compared with control mice [68]. Similarly, another study demonstrated that older mice have decreased olfactory neurogenesis and reduced odour discrimination, and that mice heterozygous for a mutation for the leukaemia inhibitory factor receptor also have both reduced olfactory neurogenesis and fine odour discrimination [69]. Furthermore, the survival, but not the proliferation, of these cells can be influenced by rearing mice in an odour-enriched environment that was associated with an improved performance on an olfactory memory task, whilst producing no difference in hippocampal neurogenesis or on a spatial (i.e., hippocampal-dependent) memory task [70], thus, under natural conditions it appears that neural precursor cells in the SVZ are only involved with olfaction, as might be anticipated from their migratory course.

2.2.2 Response of endogenous NPCs to injury

A variety of neurological insults, including physical trauma, ischaemia/stroke, hypoxia, seizures, demyelination and chronic neurodegenerative disease, result in cell loss and dysfunction, and in rodent models of these disorders NPCs appear to be quite responsive, with generally an increase in neurogenesis (see **Table 1**). There are no studies at present that have established whether similar changes in response to acute injuries occur in the human brain, although chronic neurodegenerative conditions are being studied.

On the other hand, neurogenesis in transgenic mouse models of various neurodegenerative disorders is generally decreased. For example, in both the R6/1 and R6/2 mouse models of HD there is decreased proliferation of NPCs in the dentate gyrus [71,72]. However, in two studies by Faull *et al.*, postmortem examination of patients with HD has demonstrated that there is increased proliferation and neurogenesis in the subependymal layer (SEL) compared to non-HD brains, without any comment on neurogenesis in the dentate gyrus [73,74]. There was also a correlation between the number of proliferating cells in the SEL (as determined by PCNA staining) and the grade of pathology, with more proliferation in those brains with the greatest pathology. The subependymal layer lies beside the striatum where the majority of the pathology occurs in HD and, therefore, these cells are well-placed to respond to cell loss, if that is indeed what they do.

A transgenic mouse model of PD expressing α-synuclein has a similar rate of NPC proliferation but decreased survival compared to non-transgenic control mice [75]. In postmortem human tissue there also appears to be decreased proliferation in both the SVZ and the dentate gyrus of PD patients compared to controls [76], whilst there is an increase in polysialic acid (PSA)-like immunoreactivity in the substantia nigra of PD patients that is indicative of newly differentiated neurons [77].

The results are more ambiguous in models of AD. Transgenic mouse models of the mutated amyloid precursor protein (APP) have less BrdU labelled cells in the SVZ [78] and hippocampus compared to control mice [79]. In the first study, injecting the amyloid-β (Aβ) peptide into the lateral ventricle also caused a decrease in BrdU labelled cells in the SVZ, which is in agreement with work on the mouse model carrying the *APPsw* (*Tg2576*) mutant gene [80]. However, a similar *APPsw* transgenic mouse model showed an increase in neurogenesis in the hippocampus and SVZ [81]. Using transgenic mouse models of presenilin-1, Wen *et al.* have demonstrated that overexpression of human wild-type presenilin-1 increases neurogenesis, whilst expression of mutant presenilin-1 (P117L) impairs neurogenesis [82,83]. This is in contrast to another recent study that has shown that wild-type presenilin-1 reduces proliferation of NPCs by inhibiting β-catenin, whilst mutant presenilin-1 (A246E) increases proliferation [84]. The discrepancy may be due to the different mutant forms of presenilin-1 used in the experiments. In humans, only one study has examined neurogenesis in the AD brain, and was done indirectly by looking at protein levels of immature neural markers in the hippocampus using western blots. The study found an increased expression of immature neural markers suggesting an increase in neurogenesis [85].

To summarise, there is evidence that neurogenesis can be increased in response to a wide variety of acute injuries in a

Table 1. Factors that have been reported to influence some aspect of neurogenesis in the hippocampus or subventricular zone *in vivo* .

Stimulus	Effect	Ref.
Lesions		
MCAO/ischaemia/stroke	↑	[86,101-104]
Seizure	↑	[105]
Demyelinating lesion	↑	[106,107]
Physical trauma	↑	[108,109]
Other	↑	[34]
Growth factors		
IGF-1	↑	[98,110-112,204]
VEGF	↑	[99,113,114,205]
BDNF	↑	[100,115-117]
TGFα	↑	[157]
EGF	↑	[118]
FGF-2	↑	[118]
CNTF	↑	[119]
PDGF	↑	[120,206]
EPO	↑	[121,206]
Antidepressants/mood stabilisers		
Fluoxetine	↑	[122]
Lithium	↑	[57]
Imipramine	↑	[58]
Valproate	↑	[123,207]
Hormones		
Prolactin	↑	[124,208]
Oestrogen	↑	[125,209]
DHEA	↑	[126]
19-Nortestosterone	↓	[127]
Corticosterone	↓	[128]
Neurotransmitters*		
Dopamine	↑	[76,129,130]
Serotonin	↑	[60,61,62]
Acetylcholine	↑	[131]
Glutamate	↓	[132,133]
Noradrenaline	↑	[134]
Nitric oxide	↓	[135,210]
Neuropeptide Y	↑	[136]

*Neurotransmitters, neuropeptides, or their agonists/antagonists.
(↑) Increased neurogenesis; (↓) Decreased neurogenesis.
BDNF: Brain-derived neurotrophic factor; CNTF: Ciliary neurotrophic factor; DHEA: Dehydroepiandrosterone; EGF: Endothelial growth factor; EPO: Erythropoietin; FGF: Fibroblast growth factor; GIP: Glucose-dependent insulinotropic polypeptide; IGF: Insulin-like growth factor; MCAO: Middle cerebral artery occlusion; PACAP: Pituitary adenylyl cyclase-activating polypeptide; PDGF: Platelet-derived growth factor; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor.

Table 1. Factors that have been reported to influence some aspect of neurogenesis in the hippocampus or subventricular zone *in vivo* (Continued).

Stimulus	Effect	Ref.
Neurotransmitters* (Continued)		
GIP	↑	[137]
PACAP	↑	[138,211]
Environmental factors		
Physical activity	↑	[48,139-141]
Environmental enrichment	↑	[70,142-144]
Learning	↑	[55]
Dietary restriction	↑	[115,145]
Stress	↓	[146-148]
Transgenic animal models		
Huntington's disease	↓	[71,72]
Parkinson's disease	↓	[75]
Alzheimer's disease	↓	[82,81,149]

*Neurotransmitters, neuropeptides, or their agonists/antagonists.
(↑) Increased neurogenesis; (↓) Decreased neurogenesis.
BDNF: Brain-derived neurotrophic factor; CNTF: Ciliary neurotrophic factor; DHEA: Dehydroepiandrosterone; EGF: Endothelial growth factor; EPO: Erythropoietin; FGF: Fibroblast growth factor; GIP: Glucose-dependent insulinotropic polypeptide; IGF: Insulin-like growth factor; MCAO: Middle cerebral artery occlusion; PACAP: Pituitary adenylyl cyclase-activating polypeptide; PDGF: Platelet-derived growth factor; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor.

range of animal models (**Table 1**; see [56] for a recent review). It is tempting to conclude that the NPCs are responding in order to heal the damaged brain, much like skin cells proliferate, migrate and differentiate to heal cutaneous wounds. However, there is no direct evidence thus far that these newly divided cells contribute in any substantial way to recovery. This is not surprising as the actual number of cells comes nowhere near to replacing those that have been lost. For example, in a mouse model of stroke, only 0.2% of the lost neurons were replaced 6 weeks after the insult [86]. Alternatively, NPCs may not be responding to specific insults but may simply have a non-specific response to the various environmental cues caused by injury. Determining whether the brain is attempting to repair itself or whether alterations in neurogenesis in response to injury is simply an epiphenomenon will have implications for future treatments as it will likely be easier to enhance an already existing repair mechanism than to co-opt a non-specific response for a therapeutic purpose.

2.2.3 Endogenous NPCs can be influenced by environmental and chemical factors

In addition to being responsive to injury, endogenous NPCs can be influenced by a bewildering number of endogenous and exogenous chemical factors as well as environmental and

genetic factors (see **Table 1** for a partial list). In addition to the various lesions and transgenic models mentioned above, endogenous factors, including numerous growth factors, many major neurotransmitters and hormones, can influence adult neurogenesis to a great extent. Environmental factors include dietary restriction, physical activity, living in an enriched environment and learning. Other factors include ethanol [87,88], statins [89], irradiation [90,91], inflammation [92,93], sildenafil citrate (Viagra®) [94] and even ginseng [95]. Age has perhaps one of the largest influences on neurogenesis, with older animals having much less proliferation [96,97]. Not all of these factors are independent of each other. For example, running increases neurogenesis [48], which is mediated by IGF-1, VEGF and BDNF-growth factors [98-100]. Therefore, despite the seemingly large number of factors influencing neurogenesis, there are likely a few final common pathways by which neurogenesis is regulated.

2.2.4 *Relevance to humans*

It should be stressed that most of the work described above has been conducted in rodents and the applicability of these findings to humans needs to be established. It has been shown, however, that neurogenesis occurs in the adult human brain using the mitotic marker BrdU together with neural markers, which has become the standard technique to label new neurons in animal studies [150]. Cells can be extracted from the adult human brain, propagated in culture and differentiated into different neuronal cell types, demonstrating that multipotent cells exist in adult humans [151,152], but the behaviour of these cells *in vivo* still has to be determined. For ethical reasons it is not possible to replicate most of the animal studies in humans, particularly those involving the manipulation of NPCs. It has been demonstrated, however, that irradiating the brains of mice decreases neurogenesis and that analogous low-dose therapeutic irradiation in humans for the treatment of brain tumours causes defects in hippocampal-dependent functions, such as learning and memory, in both paediatric and adult populations [153]. Although still a hypothesis at this point, it is possible that irradiation of human brains decreases neurogenesis (as it does in rodents) and this contributes, in part, to the observed cognitive dysfunction in patients who have undergone this treatment.

It appears that the structure of the human SVZ is different from other animals studied. The human SVZ is organised differently and is characterised by an astrocytic ribbon and lacks chains of migrating neuroblasts in the SVZ or in the pathway to the olfactory bulb [154]. However, there does appear to be ongoing neurogenesis in the human olfactory system [155], highlighting that whilst the general principles of neurogenesis may be the same across mammalian species the exact details of how this is achieved may vary.

2.2.5 *Therapeutic potential*

It is interesting to speculate that we have been modifying neurogenesis for a number of years towards therapeutic ends without knowing it. As mentioned above, antidepressant drugs and electroconvulsive therapy could be working, in part, by increasing neurogenesis in the hippocampus. Similarly, some drugs for AD work by increasing acetylcholine levels and acetylcholine increases neurogenesis, perhaps accounting for some of the effects of these drugs [131]. Furthermore, dopamine receptor agonists are used for the treatment of PD and have been shown to increase proliferation in the SVZ [76], although reproducibility of this effect is debated [156]. It would be of greater interest, however, to establish that NPCs can be manipulated to do far more, such as replace cells that have been lost through acute trauma or a chronic degenerative process.

Towards this end, Fallon *et al.* have shown that infusion of transforming growth factor α (TGFα) into the rat striatum increased proliferation of cells in the SVZ [157]. These cells migrated into the striatum, differentiated into tyrosine hydroxylase-expressing neurons, and improved motor performance in a mouse model of PD. Nevertheless, using a similar protocol, Cooper and Isacson have only been able to replicate the induction of proliferation and migration of SVZ cells, but not the differentiation into dopaminergic neurons and the amelioration of motor deficits [158]. In addition, the rats given TGFα infusions in the Cooper study developed hyperplastic nodules in the medial, lateral and dorsal walls of the SVZ seven days after infusions, which raises concerns of uncontrolled cellular proliferation.

Another group has increased neurogenesis in the SVZ by using viral vectors to simultaneously express BDNF (increasing proliferation), and noggin (driving cells towards a neural fate) in SVZ cells [159,212]. These cells migrated into the striatum, differentiated into medium spiny neurons and sent axons to their usual targets such as the globus pallidus. No behavioural tests were conducted in this study, but based on the circuit reconstruction achieved by the medium spiny neurons it would be a logical step to test the efficacy of the approach in a mouse model of HD. Regeneron Pharma has patented this approach for the treatment of HD together with similar approaches for the treatment of PD, amyotropic lateral sclerosis, multiple sclerosis, stroke and traumatic injury to the brain and spinal cord [212]. In a mouse model of stroke, Arvidsson *et al.* demonstrated that neural precursor cells from the SVZ increase their rate of proliferation and migrate into the striatum in response to a middle cerebral artery occlusion [86]. These cells expressed mature neural markers, including DARPP-32, suggesting that they differentiate into medium spiny neurons. In another ischaemic model Nakatomi *et al.* demonstrated that infusion of EGF and FGF-2 into the lateral ventricles of rats increased proliferation of neural precursor cells [160]. These replaced the cells in the CA1 region of the hippocampus that were lost due to the insult, formed connections with existing cells and ameliorated deficits in hippocampal-dependent spatial cognitive performance. Therefore, it does appear that in animal models NPCs can be manipulated

in vivo to achieve circuit reconstruction and improve behavioural outcomes.

Therefore, it is not surprising that biotech companies are attempting to find ways of increasing neurogenesis in adult mammals. Stem Cell Therapeutics, Inc. is a leader in the field with patents on the use of erythropoietin [206], pituitary adenylyl cyclase-activating polypeptide [211], IGF-1 [204] and prolactin [208] for the treatment of various neurological disorders. In addition, NeuroNova AB has claims on platelet-derived growth factor and VEGF [205] and agents that increase intracellular cAMP or Ca^{2+} levels [213]. Neurostasis, Inc. has patented oestrogen for the same purpose [209], and Neotherapeutics, Inc. has claimed the use of purine analogues and other molecules to stimulate neurogenesis [214]. In addition, antipsychotic agents such as atypical neuroleptics have been patented for the use of treating some neurodegenerative disorders together with schizophrenia and attention-deficit disorder by means of increasing neurogenesis [207]. As neurogenesis can be compromised by irradiation [90] and can be restored by blocking neuroinflammation [92], the use of anti-inflammatory agents has been claimed as a means of treating individuals subjected to cranial irradiation (as part of their anticancer therapy), for the treatment of various neurodegenerative disorders, or for acute injuries [215]. Van Praag and Gage discovered a synergistic action between physical exercise and the administration of either a flavonoid or an antioxidant to increase neurogenesis. This combination has been claimed as a method for increasing neurogenesis and for improving cognitive performance under both pathological and non-pathological conditions such as in sleep-deprived individuals [216].

There are some potential difficulties and drawbacks to using this approach for the treatment of neurodegenerative disorders. The ideal treatment would involve manipulating NPCs pharmaceutically by oral administration of the drug; which is easy to administer, the dose can be readily modified to suit individual patients, and treatment can be easily discontinued if side effects arise. However, other methods might include infusing growth factors directly into the brain via a cannula, or using gene therapy to transfect cells so that they produce the factors of interest. One potential risk of any method used is excessive and uncontrolled proliferation of NPCs. Too much neurogenesis might disrupt existing neural circuits, as suggested by some of the seizure literature (see [161] for a review), or worse, lead to an increased risk of tumour formation. As NPC proliferation and neurogenesis cannot be monitored in humans, uncontrolled growth may go unnoticed until side effects manifest themselves. In addition, infusing growth factors via a cannula has minor surgical risks whilst a gene therapy approach, as mentioned earlier, runs the risk of insertional mutagenesis [19].

3. Expert opinion

Transplanting cells into the brain and stimulating endogenous neural precursor cells are two cell-based approaches that are being developed for the treatment of various neurological disorders. Each has its strengths and weaknesses. For example, it is possible to transplant cells into most regions of the brain, making this approach more flexible than manipulating neurogenesis, which only occurs in a few specific regions (under normal physiological conditions). The transplantation approach, however, is limited by the supply of cells, both in terms of numbers and quality, whilst endogenous NPCs are already conveniently located in the brain. Thus, as these two therapeutic approaches develop, they may find different applications.

The sobering results of two recent double-blind placebo-controlled clinical trials in neurotransplantation in PD have decreased enthusiasm for this approach and attention is therefore turning to endogenous neural precursor cells. As stated earlier, most of the work examining NPCs has been conducted in animal models, and in rodents in particular. Therefore, one has to be careful when translating these findings to humans, as there appear to be significant differences between humans and other mammals, such as in the organisation of the subventricular region and rostral migratory stream [154]. Therefore, it is anticipated that future work will involve translating the results of animal models to humans and further work needs to be done to better understand the signalling pathways and factors involved; which factors can influence neurogenesis, and the extent to which neurogenesis accounts for behavioural changes above that which can be attributed to other changes (e.g., in LTP, gene transcription etc.). In addition, the ability to manipulate NPCs in humans, either with environmental modifications, infusion of growth factors, or introducing novel genes via viral or non-viral means [19] will be critical for therapeutic advances. Through these advances it is hoped that research into adult neurogenesis will find its way into the clinic for the treatment of numerous patients who suffer from a range of debilitating neurological conditions.

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