OPINION

The therapeutic potential of neural stem cells

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Abstract | Recent evidence shows that transplantation of neural stem/precursor cells may protect the central nervous system from inflammatory damage through a 'bystander' mechanism that is alternative to cell replacement. This novel mechanism, which might improve the success of transplantation procedures, is exerted by undifferentiated neural stem cells, the functional characteristics of which are regulated by important stem cell regulators released by CNS-resident and blood-borne inflammatory cells. Here, we discuss this alternative bystander mechanism in the context of the atypical ectopic perivascular niche. We propose that it is the most challenging example of reciprocal therapeutic crosstalk between the inflamed CNS and systemically transplanted neural stem cells.

Neural stem/precursor cells (NPCs) are a heterogeneous population of mitotically-active, self-renewing and multipotent cells of both the developing and the adult CNS, and show complex patterns of gene expression that vary in space and time[1–3] (BOX 1; FIG. 1a). In the late sixties, proliferating neural cells — possibly representing newly generated neurons — were identified in the adult rat brain[4,5]. Since then, NPCs have been isolated from the entire embryonic as well as the adult CNS. The ganglionic eminence(s) in the embryo, and both the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) in the adult have consistently been shown to contain stem-cell-like precursors capable of driving neurogenesis and gliogenesis[2,6]. These regions were then defined as highly specialized CNS germinal niches[7] (FIG. 1a), which contain slowly-proliferating putative CNS stem cells immunoreactive for glial fibrillary acidic protein (GFAP), nestin, and, eventually, the radial glia marker RC2 (REFS 8–11; BOX 1).

Soon after the *in vivo* identification of stem cells from the CNS, different procedures were developed to allow us to safely expand and maintain these cells in chemically defined media for years[12]. As a consequence, protocols to obtain a large number of NPCs *in vitro* have been established, thereby supporting the concept that these cells might represent a renewable source of uncommitted ready-to-use cells for transplantation purposes[13] (BOX 2). NPC-based therapies for nervous system disorders — for example, stroke, Parkinson's disease, Huntington's disease, multiple sclerosis and spinal cord injury (SCI) — have been successfully developed. Although most of these attempts have succeeded in experimental models, there are still important issues that need to be resolved before any potential applications of such promising therapies in humans can be foreseen. Not only the ideal cell source for transplantation (embryonic versus adult), but also the best route for cell administration (local versus systemic) have to be determined. However, the putative mechanism(s) that sustain both repair capabilities as well as long-term functional integration of NPCs upon transplantation are not clear. Although there are indications that stem cells can reach the target organ and differentiate into the appropriate lineage, evidence that transplanted NPCs can reconstruct the three-dimensional brain architecture and give rise to large numbers of properly functioning cells integrating into the brain circuitries is still scarce.

In this article, we first consider the limited efficacy of endogenous adult (or somatic) NPCs in promoting brain repair, and then focus on transplantation of adult NPCs (aNPCs) — from embryonic, foetal or adult CNS tissue sources — as a therapeutic measure through which to overcome the limited repair capabilities of the CNS. Acute and chronic inflammatory CNS disorders are either characterized by the primary inflammation that leads to secondary neurodegeneration (for example, multiple sclerosis, SCI, brain trauma and stroke), or by the primary neurodegeneration that is accompanied by secondary reactive inflammation (for example, Parkinson's disease, epilepsy and Huntington's disease). We analyse both types of disorder in order to discuss recent evidence supporting the concept that CNS inflammation, on the one hand, represents the likely mechanism underlying the limited repair capabilities of endogenous aNPCs but, on the other hand, provides the ideal environmental framework to promote repair via transplanted aNPCs. We consider the ideal cell source of aNPCs, the best route for transplantation and the mechanism(s) — that is, cell replacement versus bystander neuroprotection — that underlie the therapeutic efficacy of transplantable aNPCs. Finally, we discuss the new and provocative concept of non-conventional reconstitution of the endogenous stem cell compartment through the establishment of the atypical ectopic (perivascular) niche following intravenous aNPC transplantation.

Endogenous aNPCs for CNS repair

Endogenous aNPCs residing in germinal niches might be beneficial to nervous system repair owing to their ability to support neurogenesis and gliogenesis during adulthood[14]. Nevertheless, self-renewal, proliferation, differentiation and migration of these cells vary, depending on the local microenvironment that characterizes the

Box 1 | **Germinal (neurogenic) stem cell niches of the adult mammalian brain**

Neural stem/precursor cells. Adult CNS stem cells show cardinal features, such as unlimited capacity for self-renewal, indefinite ability to proliferate in response to mitogens, and multipotency for the different neuroectodermal lineages of the CNS. Multipotent progenitors of the adult brain are proliferative cells with only limited capacity for self-renewal that can differentiate into at least two different cell lineages[78]. Lineage-specific precursors or progenitors are cells that are restricted to one distinct lineage (such as neuronal, astroglial or oligodendroglial). Together, CNS stem cells and all types of precursor/progenitor are, broadly speaking, neural precursor cells (NPCs). We use NPCs as a generic term encompassing both stem and early progenitor cells (FIG. 1a).

The germinal niche. Self-renewal and differentiation of NPCs are regulated by a specialized microenvironment — conventionally referred to as the germinal niche — in which these cells reside. Both environmental cues and intrinsic genetic programmes are required to maintain stem cell properties and to direct, or regulate, stem cell proliferation and differentiation within niches[6].

Cytoarchitecture of the niche(s). The subventricular zone (SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus are brain germinal regions in which neural stem cells reside and support neurogenesis and gliogenesis throughout adult life (FIG. 1). Cells with structural and molecular characteristics of astrocytes are the neurogenic entities (true stem cells or type-B cells) in the SVZ and SGZ[8,10,79]. The SVZ astrocytes, which express glial fibrillary acidic protein (GFAP), are in intimate contact with all other SVZ cell types, including the rapidly dividing transit amplifying (type-C) cells and the lineage-committed (postmitotic) migratory neuroblasts (type-A cells). The cell lineage differentiation pathway goes from type-B, through type-C to type-A cells, with type-B cells believed to be the self-renewing primary precursors[10]. In the SGZ, GFAP-expressing astrocytes function as stem (type-B) cells, and undergo self-renewal, proliferation and differentiation into transit-amplifying (type-D) cells, which then differentiate into lineage-committed migratory granule neurons (type-G cells)[80,81]. The maintenance and differentiation of neural stem cells in brain niches seems to depend on their physical contact with the basal lamina, which acts as a scaffold as well as sequestering and/or modulating cytokines and growth factors derived from local cells (such as fibroblasts, macrophages and pericytes)[82]. Type-B cells in the SVZ are in close contact (interdigitated) with both the basal lamina and the blood vessels. In the SGZ, bursts of endothelial cell division are spatially and temporally related to clusters of neurogenesis[80].

different types of CNS injury (for example, acute versus chronic, focal versus multifocal)[15–18]. The presence of nestin-reactive proliferating progenitor cells in the area between the damaged tissue and the surrounding intact cerebral parenchyma has been shown, one week after the pathogenic event, in experimental models of acute focal inflammatory CNS disorders such as SCI and stroke[18–22]. In experimental models of chronic inflammatory multifocal demyelinating disorders such as experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis, mitotically active progenitor cells, which reside in either the SVZ of the brain or the subependymal layer of the central canal of the spinal cord, subvert their physiological destiny. They either migrate longitudinally along the rostral migratory stream (RMS) to the olfactory bulb, or radially to the lateral columns of the spinal cord, and migrate into areas of demyelination where they differentiate into glial cells[16,17].

However, although accumulating evidence indicates that endogenous neurogenesis and gliogenesis occur as part of an 'intrinsic' self-repair process during the course of inflammatory CNS disorders, there are no convincing explanations about the overall incapacity of the endogenous stem cell compartment to promote full and long-lasting CNS repair. Recent data suggest that inflammatory components, such as CNS-infiltrating blood-borne inflammatory mononuclear cells, reactive CNS-resident cells (for example, astrocytes, brain endothelial cells and microglia) and humoral mediators (for example, cytokines and chemokines), can be responsible for such failure. This is because they can affect proliferation and differentiation of aNPCs (TABLE 1; FIG. 1b), either directly or indirectly through the aberrant (uncoordinated) re-expression of developmental genetic programmes that regulate stem cell behaviour.

This hypothesis is supported by the following evidence, which is mostly accumulated from studies using experimental models of chronic (EAE) and subacute (induced by lipopolysaccharide, LPS) CNS inflammation. Activated encephalitogenic lymphocytes and reactive CNS-resident cells from EAE mice, which cause patchy demyelination and coexist in the same inflamed perivascular CNS areas, secrete bone morphogenetic protein 4 (BMP4) and its antagonist noggin — two major stem cell fate regulators of the stem cell niche in the SVZ[23–27]. Sonic hedgehog (SHH), which is generated in the ventral neural tube during embryonic CNS development to promote the formation and identity of the ventral interneuron progenitors[28], is re-expressed in inflammatory demyelinated lesions in rats with EAE[29]. Notch and jagged, which are crucial for axonal patterning and myelination during embryogenesis[30], are expressed at the lesion borders of inflammatory demyelinating lesions in patients with multiple sclerosis[31]. However, their expression in demyelinating diseases might be of limited functional significance, as was recently demonstrated using the inducible *Cre-Lox* technologies to remove Notch from precursor cells[32]. During subacute LPS-induced brain inflammation, interleukin-6 (IL-6) released by microglia significantly impairs neurogenesis in the hippocampus *in vivo*. However, the impairment is fully restored when non-steroidal anti-inflammatory drugs (such as indomethacin) are used[25]. *In vitro* generation of new neurons and oligodendrocytes from aNPCs is induced and supported by mouse microglia that have encountered T-cell-associated cytokines, such as interferon-γ (IFNγ) and IL-4, but blocked by those that have encountered endotoxins, such as LPS[24]. In a mouse model of acute ischaemic stroke, there is a transient increase in the proportion of SVZ cells that undergo symmetric cell division (as opposed to asymmetric cell division), and an increase in the incidence of neuronal differentiation[20]. In immune-deficient mice, hippocampal neurogenesis is markedly impaired and can be restored by T cells reacting against brain autoantigens (such as myelin basic protein, MBP)[33].

Taken together, these results have prompted us to speculate that in certain chronic CNS inflammatory disorders (such as multiple sclerosis), regional tropism for niche-like areas of blood-borne inflammatory cells might occur (FIG. 1b) as a consequence of the capacity of the cell components of the niche to secrete molecules that preferentially attract inflammatory cells. This, in turn, supports the idea that these disorders can be viewed as dysfunctions of stem cells rather than as caused by an uncontrolled, and still undiscovered, pathogenic alien(s). Although the discussion about neural progenitors, which reside outside canonical germinal niches and are able to generate astrocytes, oligodendrocytes and neurons in response to

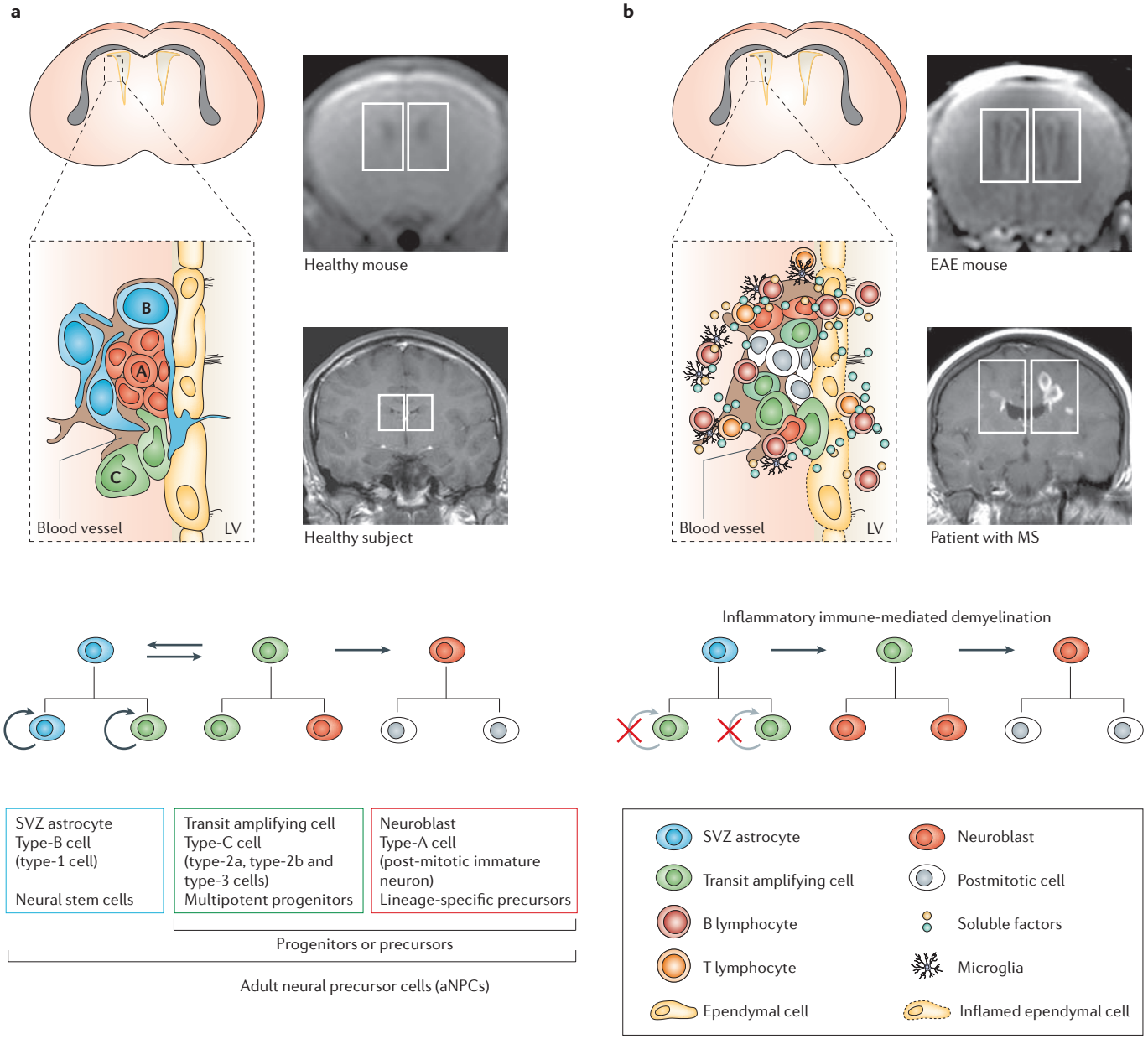

Figure 1 | **Cytoarchitecture of the niche(s) in the subventricular zone of the healthy and chronically inflamed adult brain. a** | In both rodents[10,105] and humans[106,107], the healthy subventricular zone (SVZ) of the lateral ventricle (LV) wall contains bona fide stem cells and progenitors that are in intimate contact with ependymal cells and blood microvessels. Cell proliferation and differentiation in this prototypical germinal niche depend on the physical contact between the lineage-committed (post-mitotic) migratory neuroblasts (type-A cells), true stem cells (type-B cells) and rapidly dividing transit amplifying cells (type-C cells), the basal lamina and brain microvessels. In the right-hand side insets, gadolinium-enhanced T_1-weighted magnetic resonance images of both a healthy rodent and human show the healthy periventricular (SVZ) region. The bottom panel shows that the lineage differentiation pathway goes from type-B, through type-C to type-A cells, with type-B cells believed to be the self-renewing (indicated by circular arrows) primary precursors. **b** | The SVZ in the inflamed CNS of a patient with multiple sclerosis (MS) and its experimental rodent counterpart, experimental autoimmune encephalomyelitis (EAE). The CNS-infiltrating blood-borne encephalitogenic immune cells (such as monocytes, and T and B lymphocytes) home preferentially within perivascular areas surrounding brain ventricles, where they form periventricular inflammatory demyelinating lesions. CNS-resident microglia are, in turn, activated. Inflammatory-driven changes of the appropriate temporal and spatial relationship between cells residing in the niche favouring terminal differentiation (such as generation of postmitotic cells), rather than self-renewal of stem cell elements, can be inferred. This process depends on the secretion in deranged perivascular CNS niches of soluble factors (see also TABLE 1). Histological studies show that inflammatory demyelinating lesions, which usually appear as wedge-shaped in coronal sections, with a broad base towards the ventricles, are frequently visible along the ventricular lining as elongated grey 'sleeves'. They are normally close to subependymal veins, and are often associated with a granular ependymitis[108]. The right-hand panels show gadolinium-enhanced T_1-weighted magnetic resonance images from both C57Bl/6 EAE mice at 20 days after immunization with the myelin-oligodendrocyte glycoprotein (MOG) peptide p35–55 and from patients with MS. The images show significant ependymal (upper panel) and/or parenchymal (lower panel) gadolinium enhancement (white signal) in the periventricular brain region, which suggests the presence of site-specific inflammation. The bottom panel shows that, under inflammatory conditions, type-B cells might lose their ability for self-renewal.

Box 2 | **Large-scale sources of neural stem cells for CNS repair**

Embryonic stem (ES) cells. Pluripotent cells that are derived from the inner cell mass of blastocyst stage embryos. They have two unique characteristics: an indefinite capacity for self-renewal and pluripotency, and the ability to generate all tissues of the body that are products of the epiblast lineage[83–86]. ES cells remain genetically normal even after 140 cycles of division[87]. Improvements regarding the ES culturing protocols to generate a large number of transplantable ES cells have recently been described. Feeder-independent growth of human ES cells (for example, using protein components solely derived from recombinant sources or purified from human material) can be achieved[39,40], as can the *in vitro* propagation (through continuous asymmetric cell division) of ES cell-derived neural stem cells without accompanying differentiation[88]. However, protocols for avoiding teratocarcinoma formation *in vivo* after transplantation of ES or ES-derived cells are still lacking[38]. Nevertheless, transplantation of both ES cells and ES cell-derived neural (neuronal or glial) progenitors[89,90] is able to efficiently promote CNS regeneration in preclinical models of stroke[91], myelin deficiency[92], acute spinal cord injury[93,94] and Parkinson's disease[95,96].

Adult neural stem/precursor cells (aNPCs). Multipotent cells obtainable from embryonic, foetal, neonatal or adult CNS tissues. In serum-free cultures with epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2), NPCs proliferate almost indefinitely and form multicellular free-floating spheres (neurospheres), which spontaneously differentiate into postmitotic CNS daughter cells (such as neurons, astrocytes or oligodendrocytes) after withdrawal of growth factors[41]. Human aNPCs do not show telomerase activity and have limited proliferation capacity over serial passaging *in vitro*[97]. Transplantation of native (non-immortalized) human and rodent aNPCs has been shown to significantly ameliorate experimental multiple sclerosis[27,44,45], stroke[70], Parkinson's disease[59], Huntington's disease[62] and spinal cord injury[64,66].

Oncogene-immortalized neural progenitors. Continuous cell lines of embryonic brain cells obtained by reversible oncogene transfection (allowing the replicative signal to be turned off). Different culturing protocols are available for embryonic cells obtained from different regions and developmental stages of the brain as well as for foetal and adult cells (see TABLE 2 for examples of immortalized cell lines — C17.2-CD, HB1.F3 and MHP36). As an example, *v-myc*-immortalized cerebellar mouse C17.2-CD cells have been shown to efficiently ameliorate clinicopathological features of rodent models of brain trauma[98], spinal cord injury[68], stroke[71] and Parkinson's disease[60].

Other sources. It has recently been shown that terminal neural differentiation can also be seen with non-CNS-derived multipotent somatic stem cells, such as bone marrow stem cells[99], mesenchymal stem cells[99,100], placental cord blood stem cells[101], skin stem cells[102] and adipose tissue stem cells[103,104].

environmental cues (such as oligodendrocyte precursor cells, OPCs), is beyond the scope of this article, it is worthwhile emphasizing that these precursors might also be hampered in their capacity to promote CNS repair by chronic inflammatory process (for a review, see REF. 34).

aNPC transplantation for CNS repair

Acute and chronic CNS inflammation might perturb the anatomical and functional relationships between cell components of germinal niche(s), thereby impairing the repair capacity of the endogenous stem cell compartment. As a consequence, protocols aiming to mobilize endogenous precursors from germinal niche(s) *in vivo* might be therapeutically inefficacious in inflammatory CNS disorders[35,36]. So, transplantation of aNPCs might represent an alternative, and possibly more efficacious, therapeutic approach. In TABLE 2, we have summarized the cell source, the route for transplantation and therapeutic effects of aNPCs in acute (for example, SCI, stroke and brain trauma) and chronic (for example, multiple sclerosis) inflammatory disorders as well as in disorders characterized by chronic inflammation reactive to neurodegeneration (for example, Huntington's disease, epilepsy and Parkinson's disease).

Cell sources for aNPC transplantation. In essence, the gold-standard cell source for transplantation strategies must be plastic. Both embryonic stem (ES) cells and aNPCs might meet this criterion, as they are intrinsically able to adapt their specification fate to different environmental needs[37]. Apart from ethical considerations, the therapeutic use of ES cells is still constrained by some key issues — such as feeder-independent growth (expansion) and *in vivo* teratocarcinoma formation[38] — which need to be resolved[39,40] before any ES cell-based therapy for human application can be proposed (BOX 2). However, aNPCs might represent a ready-to-use cell source for cell-based therapies, because they can be obtained from different tissues (such as embryonic, foetal and adult) and have been widely used *in vivo* without causing tumour formation or overt toxic or other side effects[41], so far.

Route of aNPC transplantation. The route of cell administration, which represents another constraint for aNPC transplantation, is very much dependent on the CNS lesion site(s) (focal versus multifocal). On the one hand, the anatomo-pathological features of focal CNS disorders, such as Parkinson's disease or SCI, Huntington's disease, stroke and brain trauma, suggest that direct local (intralesional) cell transplantation might facilitate tissue regeneration. On the other hand, the multifocality of certain CNS disorders, such as multiple sclerosis and epilepsy, represents a major limitation for intralesional cell-transplantation approaches. Following the first observation in experimental brain tumours[42] (for a review, see REF. 43), we and others have recently shown that in multifocal CNS disorders, systemic (for example, intravenous or intrathecal) transplantation of aNPCs can be therapeutically efficacious[27,44–49] owing to the ability of transplanted cells to follow, via the blood stream or cerebrospinal fluid circulation, a gradient of chemoattractants (such as pro-inflammatory cytokines and chemokines) that occur at the site of inflammatory lesions[27,44,50,51]. While promoting interaction between transplanted aNPCs and activated endothelial/ependymal cells around inflamed CNS tissues, this chemoattractive gradient leads to selective and specific homing of transplanted cells in multifocal inflammatory CNS areas (FIG. 2). Specific homing of transplanted aNPCs has been demonstrated in SCI, epilepsy and stroke (TABLE 2). However, the exact molecular mechanism that sustains this phenomenon has been detailed only in EAE. Tethering, rolling and firm adhesion to inflamed endothelial cells, and extravasation into inflamed CNS areas (FIG. 2) are sequentially mediated by the constitutive expression of functional cell adhesion molecules (such as CD44)[27,44], integrins (such as α4, β1)[27,44,52–54] and chemokine receptors (such as CCR1, CCR2, CCR5, CXCR3 and CXCR4)[27,55,56] on the surface of aNPCs (TABLE 3).

Bystander effects of transplanted aNPCs. In experimental models of CNS inflammation, there is solid evidence to show that aNPCs survive transplantation procedures within the host, migrate specifically within the damaged tissue, and maintain their multipotency. However, scarce data support the concept that these cells give rise to terminally differentiated neural cells, which, in turn, are able to sustain a programme of CNS repair through

Table 1 | **Soluble factors involved in both the biology of NPCs and CNS inflammation**

Soluble factor	Role in NPC biology (target cells indicated in brackets)	Cell source in inflammatory conditions	References
Stem cell regulators			
Bone morphogenetic protein 4 (BMP4)	(Astro)glial differentiation	Reactive astrocytes, activated endothelial cells	110
Notch 1	(Astro)glial differentiation	Adult immature OPCs	32,111
Noggin	Neuronal fate	Reactive astrocytes, lymphocytes, activated endothelial cells	23,27,112
Sonic hedgehog (SHH)	Proliferation and maintenance within niche(s) (NPCs), cell identity and fate specification (neuronal and oligodendroglial)	Reactive astrocytes, activated endothelial cells, macrophages, myelinating oligodendrocytes	29,112–116
Tenascin C	Regulation of the niche microenvironment, (chain) migration, adhesion	Reactive astrocytes, meningeal cells, macrophages, Schwann cells	117–121
Inflammatory mediators			
CCL5/Rantes	Proliferation (NPCs)	Reactive astrocytes, activated lymphocytes, microglia/macrophages	122–124
CXCL12/stromal-derived factor-1α (SDF1α)	Chemotaxis (NPCs)	Reactive astrocytes, activated endothelial cells, meningeal cells	55,122,123, 125–127
CX_3CL1/fractalkine	Proliferation (NPCs)	Reactive astrocytes, activated lymphocytes, microglia/macrophages	122–124
Interleukin-1β (IL-1β)	Neuronal fate (dopaminergic neurons)	Reactive astrocytes, activated lymphocytes, microglia/macrophages	128–130
Interleukin-6 (IL-6) family of neurotrophic cytokines (LIF, CNTF, CT-1)	(Astro)glial differentiation	Reactive astrocytes, activated lymphocytes, microglia/macrophages	128, 131
Growth factors			
Brain-derived neurotrophic factor (BDNF)	Survival and differentiation (neuronal progenitors)	Reactive astrocytes, monocytes, T helper (1 and 2) lymphocytes, B lymphocytes, activated microglia	132–136
Ciliary neurotrophic factor (CNTF)	Survival and differentiation (neuronal progenitors)	Reactive astrocytes	137, 138
Erythropoietin	Differentiation (neuronal progenitors)	Reactive astrocytes, activated endothelial cells, microglia/macrophages	139–141
Glial-derived neurotrophic factor (GDNF)	Survival and differentiation (dopaminergic neurons and neuronal progenitors)	Peripheral blood mononuclear cells	142–144
Platelet-derived growth factor (PDGF)	Proliferation (neurons, OPCs), lineage reversion to NPCs (OPCs), chemotaxis (NPCs)	Reactive astrocytes, neurons	145–149
Transforming growth factor-β (TGFβ)	Cell fate specification (neuronal)	Reactive astrocytes, microglia/macrophages, neurons	31,150–152
Vascular-endothelial growth factor-α (VEGFα)	Proliferation (NPCs), chemotaxis (NPCs)	Reactive astrocytes, activated endothelial cells	153–156

CC/CXC/CX_3C, chemokines (ending -L); CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; LIF, leukaemia inhibitory factor; OPC, oligodendrocyte precursor cell; NPC, neural stem/precursor cell.

massive cell replacement[57]. Irrespective of the characteristics of the experimental disease, which include disease course (acute versus chronic), neuropathological features (focal versus multifocal) and the types of inflammation (primary versus reactive), functional recovery obtained by aNPC transplantation scarcely correlates with absolute numbers of transplant-derived, newly generated, terminally differentiated neuronal cells (TABLE 2). Transplantation of C17.2-CD *v-myc*-immortalized, adult SVZ-derived, or foetal (human) brain-derived NPCs into rodents with experimentally induced Parkinson's disease[58–60] or Huntington's disease[61,62] rarely gives rise to neurons that express tyrosine hydroxylase (the rate-limiting enzyme involved in the synthesis of dopamine), despite significant behavioural improvement. About 13–16% of syngenic embryonic NPCs injected into rats with 6-hydroxydopamine (6-OHDA)-induced nigrostriatal degeneration (a model of Parkinson's disease) are immunoreactive for doublecortin, an early differentiation marker of stem cells[63]. In a rodent model of Huntington's disease, only ~1% of transplanted foetal (human) NPCs differentiate into neuronal nuclear (NeuN)-positive neurons[62], although most of these NPCs display the stem cell marker nestin[61]. Similarly, mice with SCI[48,64], acute stroke[65] or intracerebral haemorrhage[46] do show some functional recovery, despite pathological evidence of preferential astroglial fate of transplanted embryonic

Table 2 | **Transplantation studies of adult NPCs in animal models of CNS disorders**

Neural stem cell	Disease model	Therapeutic mechanism		Outcome	Refs
		Cell replacement	Bystander effect		
Demyelinating disorders					
Adult NPCs*	EAE	+	+	Improved	44
Adult NPCs	EAE	+/–	+	Improved	27
Adult NPCs	EAE	Not tested	+	Improved	45
Adult NPCs	EB-X	+	Not tested	Improved	157
Traumatic brain injury					
C17.2-CD‡ NPCs	CCI	+	Not tested	Improved	98
Embryonal NPCs	CCI	–	Not tested	Improved	158
Stroke					
C17.2-CD NPCs	CCAO	+	+	Not tested	71
MHP36‡ NPCs	CCAO	+	+	Not tested	159
HB1.F3‡ NPCs	Bacterial collagenase	+	+	Improved	46
HB1.F3 NPCs	MCAO	+	+	Improved	65
Foetal NPCs	MCAO	+	+	Not tested	70
Parkinson's disease					
C17.2-CD NPCs	MPTP-induced	+/–	+	Improved	60
Foetal NPCs	MPTP-induced	–	+	Not tested	160
Foetal NPCs	MPTP-induced	–	Not tested	Not tested	161
Foetal NPCs	6-OHDA-induced	–	+	Improved	58
Foetal NPCs	6-OHDA-induced	+	Not tested	Improved	162
Embryonic NPCs	6-OHDA-induced	+	Not tested	Not tested	63
Embryonic NPCs	6-OHDA-induced	–	Not tested	Not improved	163
Adult NPCs	6-OHDA-induced	–	+	Improved	59
Huntington's disease					
Foetal NPCs	QA-induced	+/–	+	Improved	62
Foetal NPCs	3-NP-induced	+/–	+	Improved	61
Acute spinal cord injury					
C17.2-CD NPCs	Hemisection	–	+	Improved	68
C17.2-CD NPCs	Hemisection	–	+	Not tested	67
Foetal NPCs	Weight drop	+	Not tested	Improved	66
Embryonic NPCs	Weight drop	+	Not tested	Not tested	48
Adult NPCs	Weight drop	+	Not tested	Improved	64
Epilepsy					
Foetal NPCs	LCP-induced	+	Not tested	Improved	49

*Adult NPCs include cells derived from embryonic, foetal, neonatal and adult CNS tissues. ‡Nomenclatures used to define immortalized NPC lines. 3-NP, 3-nitopropionic acid; 6-OHDA: 6-hydroxydopamine; C17.2-CD neonatal cerebellum-derived; CCAO, common carotid artery occlusion; CCI, controlled cortical impact; EAE, experimental autoimmune encephalomyelitis; EB-X, X-irradiation and ethidium bromide-induced focal demyelination; HB1.F3, foetal brain-derived; LCP, lithium chloride/pilocarpine; MCAO, middle cerebral artery occlusion; MHP36, embryonic hippocampus-derived; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NPCs, neural stem/progenitor cells; QA, quinolinic acid. For further details of each experimental study discussed here see online Supplementary information S1 (table).

hippocampal, adult spinal cord-derived, or foetal HB1.F3-immortalized NPCs. In mice with experimental (bacterial collagenase-induced) intrastriatal haemorrhage[46], or with acute (transient middle cerebral artery occlusion-induced) stroke[65], most of the transplanted C17.2-CD *v-myc*-immortalized NPCs surrounding damaged CNS areas express markers (such as nestin) of undifferentiated cells. Embryonic, foetal and neonatal cerebellar NPCs injected into models of SCI do not differentiate into terminally differentiated neuronal cells[48,66–68]. In EAE, very low levels of differentiation of adult SVZ-derived NPCs into myelin-forming oligodendrocytes are accompanied by neurophysiological evidence of axonal protection and remyelination[44]. In the same context, >20% of transplanted cells that have reached the inflammatory demyelinated areas do not express differentiation markers[44].

The scarce and inappropriate terminal differentiation, as well as the propensity for maintaining an undifferentiated phenotype within host tissue, suggest that transplanted aNPCs might be therapeutically efficacious through a bystander mechanism (or mechanisms) alternative to cell replacement. A bimodal mechanism of action means that aNPCs could exert their effects through two pathways, which are orchestrated by CNS-resident cells reactive to the pathological injury (mainly astrocytes and microglia) and inflammatory blood-borne cells.

First, transplanted cells might significantly reduce scar formation and/or increase survival and function of endogenous glial and neuronal progenitors that have survived the pathological insult. This neuroprotective effect is usually accompanied by increased *in vivo* bioavailability of main neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), cilliary neurotrophic factor (CNTF) and glial-derived neurotrophic factor (GDNF). This has been demonstrated in rodents with primary inflammatory CNS disorders (such as EAE[44], SCI[67,68] and stroke[65]) as well as in rodents with neurodegenerative disorders accompanied by reactive inflammation (such as Parkinson's disease[59], Huntington's disease[61,62] and epilepsy[49]) (TABLE 2). The cellular and molecular mechanism(s) underlying this phenomenon may reside in the intrinsic characteristics of neurospheres — the *in vitro* artefactual cell entity from which transplantable aNPCs derive. Neurospheres are generated *in vitro* after weeks of

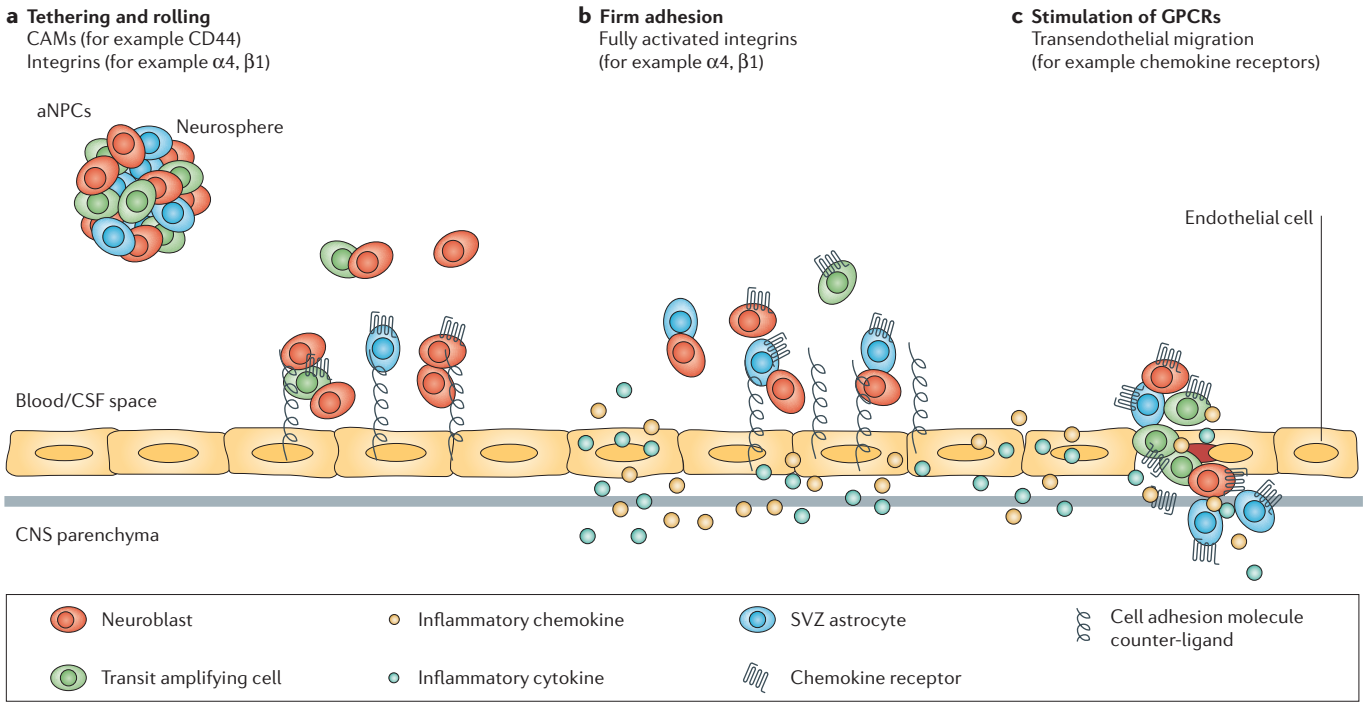

Figure 2 | **Adult neural stem/precursor cells recapitulate lymphocyte-like pathways for selective homing into inflamed areas of the CNS after intravenous injection.** A multistep model of interaction between systemically injected adult neural stem/precursor cells (aNPCs) and inflamed endothelium of the CNS. **a** | For cell adhesion and migration, aNPCs expressing cell adhesion molecules (CAMs, such as CD44) and integrins (such as α4) interact with specific ligands (hyaluronic acid and vascular cell adhesion molecule 1 (VCAM1), respectively) that are expressed by inflamed endothelial cells. **b** | To firmly adhere to and migrate across the inflamed endothelium, chemokines activate chemokine receptors (such as CCR1, CCR2, CCR5, CXCR3 and CXCR4) that are expressed on the plasma membrane of aNPCs, which induce full activation of α4 integrins. **c** | Proinflammatory cytokines and chemokines that are produced by CNS-resident cells, blood-borne inflammatory cells and transplanted aNPCs orchestrate these sequential events, and result in activation of G-protein coupled receptors (GPCRs) and migration across the endothelium. The molecular pathways used by transplanted aNPCs resemble those used by the encephalitogenic lymphocytes that accumulate at inflammatory sites during human and experimental multiple sclerosis[109] (see TABLE 3 for more details about the soluble molecules involved in this process). CSF, cerebrospinal fluid.

serum-free cell culturing in the continuous presence of high amounts of epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF2). This culturing protocol selects only for growth factor-responsive cells. On transplantation, surviving transplantable aNPCs might be much more responsive to specific (growth factor-driven) environmental signals in the target tissue that trigger the release of growth factors such as GDNF, BDNF, CNTF and NGF[61,64,67,69].

Second, undifferentiated transplanted aNPCs might promote bystander immunomodulation, as they can release soluble molecules (such as cytokines and chemokines) and express immune-relevant receptors (such as chemokine receptors and CAMs), which are able to profoundly change inflammatory environment(s) (TABLES 1,3). Transplanted aNPCs might induce apoptosis of inflammatory T lymphocytes by upregulating membrane expression of certain death receptor ligands (such as FASL, TRAIL and APO3L), as has recently been shown *in vitro* and in mice with EAE[27]. This aNPC-mediated mechanism is triggered by pro-inflammatory (T helper 1-like, IFNγ, IL-1β and tumour necrosis factor-α, TNFα), but not anti-inflammatory (T helper 2-like, IL-4, IL-5 and IL-13) cytokines. Transplanted aNPCs can also significantly and specifically downregulate effector functions of inflammatory T cells and macrophages in the target tissue. In EAE, it has been shown that the antigen-specific proliferation rate of encephalitogenic MOG (myelin oligodendrocyte glycoprotein)-reactive T lymphocytes is decreased in the presence of aNPCs[45]. In animal models of stroke, decreased infiltration of mononuclear cells has been reported at lesion borders of ischaemic areas in the CNS where aNPCs accumulate[70,71].

The results that support the bimodal bystander therapeutic role of transplanted aNPCs have recently been reinforced by evidence obtained from experimental models of chronic degeneration of retinal ganglion cells, acute cochlear ischaemia, and gastroparesis. In a gerbil model of acute cochlear ischaemia, unilateral intracochlear injection of syngenic embryonic (embryonic day (E)17–18) NPCs resulted in predominant nestin (undifferentiated) immunoreactivity of transplanted cells accompanied by increased availability of NGF and/or cytokines[72]. C17.2-CD *v-myc* immortalized NPCs, which were injected into mice with acute or chronic retinal ganglion cell degeneration, showed widespread integration and dispersion across the retina, low levels of neuronal antigen expression, and no expression of retina-specific cell markers[73]. Finally, intrapyloric transplantation of embryonic (E15) NPCs in mice with gastroparesis resulted in significant acceleration of gastric emptying. The clinical recovery was associated with widespread localization of transplanted cells at submucosal and muscular levels, predominant immunoreactivity to PGP9.5 (a neuronal marker) and GFAP (an astroglial marker), as well as with neuronal nitric oxide synthase (nNOS)-dependent restoration of pyloric sphincter nitrergic relaxation[74].

Table 3 | **Molecules used by NPCs to home in to inflamed CNS tissues**

Cell surface molecule (ligand)	Possible function in NPCs	References
α4 integrin	Adhesion to activated endothelial cells	27,44
β1 integrin	Modulation of Notch signalling within the niche, inhibition of differentiation ($\alpha_5\beta_1$)	52,164
CCR1	Migration to CCL5/Rantes	27
CCR2	Migration to CCL2/MCP1	27,165
CCR3	Quiescence, migration to CCL5/Rantes	27,124
CCR5	Unknown	27,56
CXCR3	Unknown	27
CXCR4	Survival, migration to CXCL12/SDF1α, homing into site(s) of tissue injury	27,55,56,124
CX_3CR1	Survival	56,124
CD44	Identifies an astrocyte-restricted precursor cell, adhesion to activated endothelial cells	27,44,166
PSA-NCAM	Injury-dependent migration, (oligodendro)glial differentiation, hippocampal neurogenesis	167,168
Sema-3A	Migration (repulsive) on (oligodendro)glial progenitors	169
VCAM1	Unknown	170

NPC, neural stem/precursor cell; CC/CXC/CX3C, names chemokines (ending -L) and chemokine receptors (ending -R), following the systematic nomenclature based on the position of the ligand's first two cysteine residues; CD44, CD44 antigen; PSA-NCAM, polysialylated neural cell adhesion molecule; Sema-3A, semaphorin-3A; VCAM1, vascular cell adhesion molecule 1.

The atypical ectopic niche

The next, and final, question regards the ability of transplanted undifferentiated aNPCs to exert the bystander effect long term. In certain neurological disorders characterized by recurrent and/or chronic inflammation, which invariably leads to destruction of both CNS-resident as well as transplanted cells, the propensity of transplanted aNPCs to modulate cell replacement versus bystander immunomodulatory and/or neurotrophic properties (in response to specific environmental needs) may have particular therapeutic relevance.

Recent findings in EAE studies suggest that long-term functional survival of undifferentiated aNPCs that are capable of promoting bimodal bystander neuroprotection by neurotrophic support and/or immunomodulation, can be achieved on intravenous transplantation[27,44]. This transplantation protocol promotes the formation of a new anatomical and functional entity — the atypical ectopic (perivascular) niche — which is functionally similar to prototypical germinal niches but differs in terms of cellular components and regional tropism (FIG. 3). Such atypical ectopic niches are formed around perivascular areas of the inflamed CNS (the brain and the spinal cord), and contain transplanted aNPCs (see FIG. 2 for details of pathways regulating selective and specific homing of intravenously-injected aNPCs in inflamed perivascular areas), blood-borne (encephalitogenic) inflammatory cells as well as CNS-resident cells (such as inflammation-reactive astrocytes and microglia). In response to environmental cues, the dynamic secretion of soluble inflammatory mediators, growth factors and stem cell regulators by the different cell types in the atypical ectopic niche (TABLE 1) significantly contributes to the maintenance and long-term therapeutic efficacy of (proliferating versus quiescent) transplanted aNPCs. When neuroinflammation predominates, transplanted cells retain an undifferentiated phenotype as a result of the release of BMP4 and noggin by blood-borne inflammatory cells, activated endothelial cells and astrocytes, and prevent tissue damage by inducing *in situ* programmed cell death of blood-borne encephalitogenic lymphocytes[27]. When inflammatory signals fade out and neurodegeneration prevails, transplanted cells act as bystander regulators of astrogliosis via the release of neurotrophic growth factors, thereby rescuing the ability of endogenous remyelinating OPCs[44] to proliferate and differentiate. In this case, downregulation of the environmental (inflammatory) signals that orchestrate (and contribute to) the release of stem cell regulators in the ectopic niche might induce a few transplanted cells to move out of the niche, which, in turn, acquire a mature functional phenotype and replace some damaged endogenous neural cells[27,44]. The cellular and molecular dynamic of the atypical ectopic niche might also explain the correlation between the presence of undifferentiated transplanted aNPCs in damaged tissues and the clinical recovery observed in experimental models of chronic inflammatory disorders of the CNS (TABLE 2).

Whether or not intravenously injected aNPCs also exert their bystander effect in secondary lymphoid organs (such as by inhibition of the effector function of mononuclear cells) is still under scruntiny.

Conclusions and future perspectives

In summary, the evidence reviewed in this article challenges the view that neural tem cells achieve their therapeutic efficacy exclusively by a cell-replacement mechanism. In fact, neural stem cells may also promote CNS repair through their intrinsic neuroprotective ability, which is mainly exerted by undifferentiated stem cells releasing, at the site of tissue damage, a milieu of neuroprotective molecules, temporally and spatially orchestrated by environmental needs. This milieu contains molecules (such as immunomodulatory substances, neurotrophic growth factors and stem cell regulators) that are constitutively expressed by neural stem cells for the maintenance of tissue homeostasis, both during development and in adulthood[75]. The intrinsic nature of these molecules (that is, they are pleiotropic and functionally redundant) as well as their constitutive expression by different types of stem cells (such as mesenchymal, neural and haematopoietic cells) may represent a stem cell signature. This might also reconcile data showing that other sources of somatic stem cells (such as mesenchymal stem cells and haematopoietic stem cells), with very low potential of neural differentiation or trans-differentiation, might efficiently promote CNS repair[76,77]. Therefore, cell plasticity can also be viewed as the capacity of somatic stem cells to adapt their fate and function to specific environmental needs, which arise as a result of pathological conditions — this is the idea of therapeutic plasticity. The ability of transplanted aNPCs to protect the brain from several types of injury using different and/or

multifaceted bystander strategies — the atypical ectopic (perivascular) niche being one of the most intriguing examples — is of considerable importance for the future of stem cell-based therapeutic approaches.

The knowledge of non-conventional stem cell-mediated therapeutic mechanisms might result in more efficacious therapeutic alternatives. However, we need to resolve unsolved and challenging issues about the best way to tightly control and regulate *in vivo* the different and/or multifaceted, and potentially divergent, stem cell-mediated therapeutic functions. Nevertheless, a future therapeutic scenario can be visualized in which we might be able to regulate different (conventional versus non-conventional) somatic stem cell-mediated therapeutic effects in order to treat neurological disorders more effectively without toxicity or side effects.

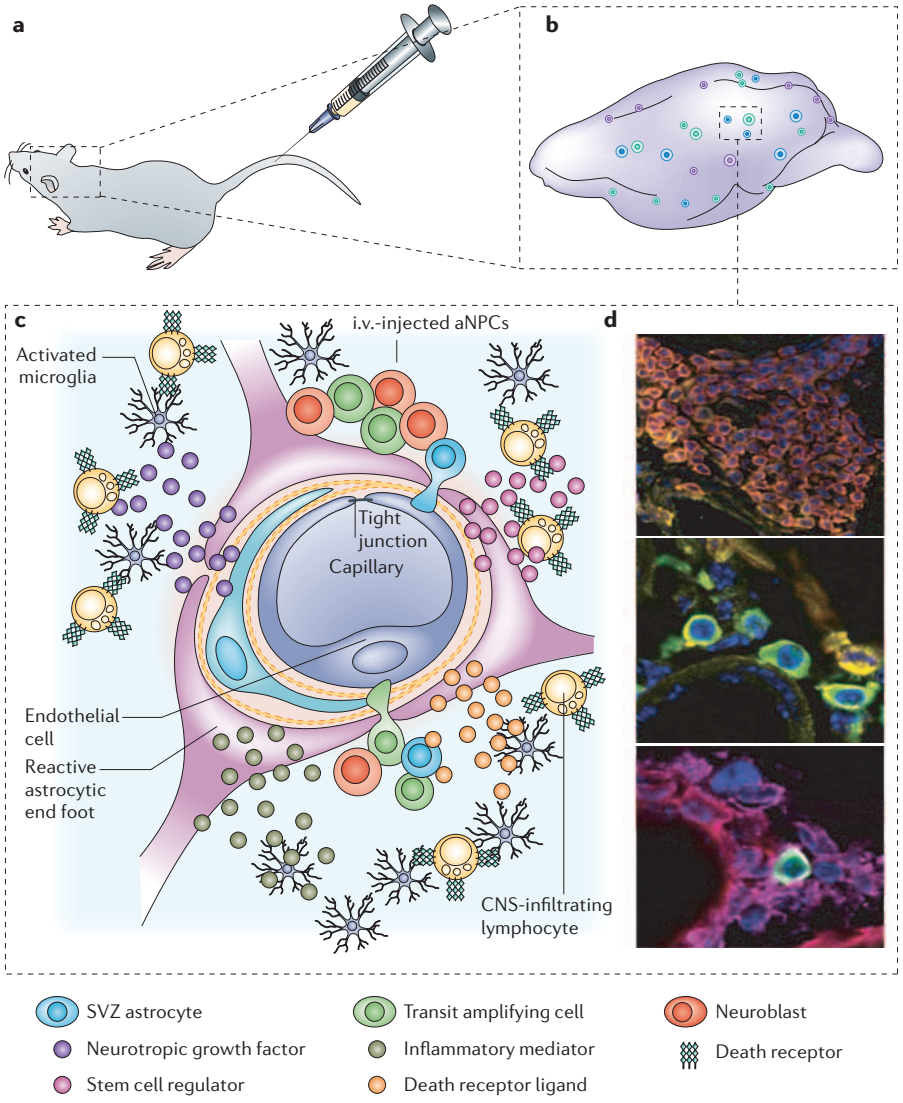

Figure 3 | **Reconstitution of the endogenous stem cell compartment via the atypical ectopic (perivascular) niche. a**,**b** | As a consequence of intravenous transplantation (**a**), adult neural stem/precursor cells (aNPCs) selectively migrate to and accumulate in the inflammatory perivascular areas in the CNS (**b**). **c** | These areas contain transplanted (via intravenous (i.v.) injection) aNPCs, blood-borne inflammatory lymphocytes, activated microglia, reactive astrocytes and inflamed endothelial cells. These newly formed entities behave as anatomically atypical, although highly specialized, ectopic niches, and are defined as atypical ectopic (perivascular) niches. Sustained crosstalk occurrs between the different cell components of the niche, and regulates long-term survival and behaviour of transplanted cells. Depending on the environmental cues, aNPCs may either remain in the niche in an undifferentiated state, thereby promoting apoptosis of neighbouring inflammatory blood-borne CNS-infiltrating lymphocytes, or move out of the niche, thereby acquiring a terminally differentiated phenotype. The environmental milieu (containing soluble inflammatory molecules, stem cell regulators and growth factors; see TABLE 1 for more details) is a key element of this dynamic process. **d** | Shows the *in vivo* appearance of the atypical ectopic (perivascular) niche in the inflamed CNS. Top: noggin (yellow)-secreting CD45-positive cells (red); middle and bottom: transplanted aNPCs (green) and CNS-resident endothelial cells (red) that secrete noggin (yellow) and bone morphogenetic protein 4 (magenta), respectively. Panel **d** reprinted, with permission, from REF. 27 © (2005) Macmillan Publishers Ltd.

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SCIENCE AND SOCIETY

Neuroscience and education: from research to practice?

Usha Goswami

Abstract | Cognitive neuroscience is making rapid strides in areas highly relevant to education. However, there is a gulf between current science and direct classroom applications. Most scientists would argue that filling the gulf is premature. Nevertheless, at present, teachers are at the receiving end of numerous 'brain-based learning' packages. Some of these contain alarming amounts of misinformation, yet such packages are being used in many schools. What, if anything, can neuroscientists do to help good neuroscience into education?

There is a hunger in schools for information about the brain. Teachers are keen to reap the benefits of the 'century of neuroscience' for their students. In neuroscience laboratories, considerable progress is being made in understanding the neurocognitive development underpinning essential skills taught by educators, such as numeracy and literacy. This progress is largely theoretical. The current gulf between neuroscience and education is being filled by packages and programmes claiming to be based on brain science. The speed with which such packages have gained widespread currency in schools is astonishing. This article highlights some pervasive 'neuromyths' that have taken root in education, gives a flavour of the information being presented to teachers as neuroscientific fact, and reviews recent findings in neuroscience that could be relevant to education. It also considers what, if anything, we should do now to influence the widespread misapplication of science to education.

Brain-based learning in schools

At a recent conference held to mark the launch of the Centre for Neuroscience in Education at the University of Cambridge[1], teachers reported receiving more than 70 mailshots a year encouraging them to attend courses on brain-based learning. Similar phenomena have been reported in other countries[2]. These courses suggest, for example, that children should be identified as either 'left-brained' or 'right-brained' learners, because individuals 'prefer' one type of processing[3]. Teachers are told that the left brain dominates in the processing of language, logic, mathematical formulae, number, sequence, linearity, analysis and unrelated factual information. Meanwhile, the right brain is said to dominate in the processing of forms and patterns, spatial manipulation, rhythm, images and pictures, daydreaming, and relationships in learning[3]. Teachers are advised to ensure that their classroom practice is automatically 'left- and right-brain balanced' to avoid a mismatch between learner preference and learning experience[3]. This neuromyth probably stems from an over-literal interpretation of hemispheric specialization.

Other courses for teachers advise that children's learning styles should be identified as either visual, auditory or kinaesthetic, and that children should then wear a badge labelled either V, A or K while in school, showing their learning style for the benefit of all of their teachers. Still others argue that adoption of a commercial package 'Brain Gym^R' ensures that 'true' education happens. Brain Gym^R prescribes a series of simple body movements[4] "to integrate all areas of the brain to enhance learning". Teachers are told that "in technical terms, information is received by the brainstem as an 'impress', but may be inaccessible to the front brain as an 'express'. This … locks the student into a failure syndrome. Whole-brain learning draws out the potential locked in the body and enables students to access those areas of the brain previously unavailable to them. Improvements in learning … are often immediate". It is even claimed that the child can press certain 'brain buttons' under their ribs[4] to focus the visual system for reading and writing.

Many in education accept claims such as these as established fact[5]. Scientists have already alerted society to the neuromyths that are dominant in education at present[6–8]. In addition to the left brain/right brain learning myth, neuromyths that relate to critical periods for learning and to synaptogenesis can be identified. The critical