

- 69 Bahr, B.A. et al. (1995) *Hippocampus* 5, 425–439
- 70 Gerfin-Moser, A. et al. (1995) *Neuroscience* 67, 849–865
- 71 Kasof, G.M. et al. (1995) *Mol. Brain Res.* 197, 197–208
- 72 Berger, T. and Frotscher, M. (1994) *J. Neurocytol.* 23, 61–74
- 73 Derouiche, A., Heimrich, B. and Frotscher, M. (1993) *Eur. J. Neurosci.* 5, 122–127
- 74 Häiler, N.P., Järhult, J.D. and Nitsch, R. (1996) *Glia* 18, 319–331
- 75 Schousboe, I. et al. (1993) *Int. J. Dev. Neurosci.* 6, 765–772
- 76 Bonnhoefer, T., Staiger, V. and Aertsen, A. (1989) *Proc. Natl. Acad. Sci. U. S. A.* 86, 8113–8117
- 77 Debanne, D., Gähwiler, B.H. and Thompson, S.M. (1994) *Proc. Natl. Acad. Sci. U. S. A.* 91, 1148–1152
- 78 Müller, D. et al. (1996) *Neuron* 17, 413–422
- 79 Charpak, S. and Gähwiler, B.H. (1991) *Proc. R. Soc. London B Biol. Sci.* 243, 221–226
- 80 Gerber, U., Lüthi, A. and Gähwiler, B.H. (1993) *Proc. R. Soc. London B Biol. Sci.* 254, 169–172
- 81 Gähwiler, B.H. and Brown, D.A. (1985) *Proc. Natl. Acad. Sci. U. S. A.* 82, 1558–1562
- 82 Gähwiler, B.H. and Brown, D.A. (1987) *Neuroscience* 20, 731–738
- 83 Charpak, S. et al. (1990) *Nature* 347, 765–767
- 84 Gerber, U. and Gähwiler, B.H. (1994) in *The Metabotropic Glutamate Receptors* (Conn, P.J. and Patel, J., eds), pp. 125–146, Humana Press
- 85 Guérineau, N.C. et al. (1995) *J. Neurosci.* 15, 4395–4407
- 86 Bossu, J.-L. et al. (1996) *J. Physiol.* 495, 367–381
- 87 Lüthi, A., Gähwiler, B.H. and Gerber, U. (1996) *J. Neurosci.* 16, 586–594
- 88 Scanziani, M. et al. (1992) *Neuron* 9, 919–927
- 89 Capogna, M., Gähwiler, B.H. and Thompson, S.M. (1993) *J. Physiol.* 470, 539–558
- 90 Thompson, S.M., Capogna, M. and Scanziani, M. (1993) *Trends Neurosci.* 16, 222–227
- 91 Capogna, M., Gähwiler, B.H. and Thompson, S.M. (1996) *J. Neurophysiol.* 75, 2017–2028
- 92 Del Río, J.A. et al. (1991) *Neuroscience* 43, 335–347
- 93 Capogna, M. et al. *J. Neurosci.* (in press)
- 94 Thompson, S.M. and Gähwiler, B.H. (1989) *J. Neurophysiol.* 61, 512–523
- 95 Rimvall, K., Keller, F. and Waser, P.G. (1987) *Acta Neuropathol.* 74, 183–190
- 95 Vornov, J.J., Tasker, R.C. and Coyle, J.T. (1991) *Exp. Neurol.* 114, 11–22
- 96 Müller, M. et al. (1994) *Hippocampus* 4, 204–209
- 97 Dailey, M.E. et al. (1994) *J. Neurosci.* 14, 1060–1078
- 98 Gähwiler, B.H. and Hefti, F. (1984) *Neuroscience* 13, 681–689
- 99 Li, D. et al. (1993) *Neuroscience* 52, 799–813
- 100 Rennie, S., Lotto, R.B. and Price, D.J. (1994) *Neuroscience* 61, 547–564
- 101 Cardoso de Oliveira, S. and Hoffman, K.P. (1995) *Eur. J. Neurosci.* 7, 599–612
- 102 Papp, E.C., Heimrich, B. and Freund, T.F. (1995) *Neuroscience* 69, 99–105
- 103 Pleniz, D. and Aertsen, A. (1996) *Neuroscience* 70, 861–891
- 104 Bergold, P.J. et al. (1993) *Proc. Natl. Acad. Sci. U. S. A.* 90, 6165–6169
- 105 Stoppini, L., Buchs, P.-A. and Müller, D. (1993) *Neuroscience* 57, 985–994
- 106 McKinney, R.A., Gähwiler, B.H. and Thompson, S.M. (1995) *Soc. Neurosci. Abstr.* 21, 23
- 107 Müller, D. et al. (1994) *Neuroscience* 61, 441–445
- 108 Heimrich, B. et al. (1996) *Neuroscience* 72, 409–417
- 109 Tasker, R.C., Coyle, J.T. and Vornov, J.J. (1992) *J. Neurosci.* 12, 4298–4308
- 110 Vornov, J.J., Tasker, R.C. and Coyle, J.T. (1994) *Stroke* 25, 457–464
- 111 Nevell, D.W. et al. (1995) *J. Neurosci.* 15, 7702–7711
- 112 Strasser, U. and Fischer, G. (1995) *Brain Res.* 687, 167–174
- 113 Li, D., Field, P.M. and Raisman, G. (1995) *Eur. J. Neurosci.* 7, 1164–1171
- 114 Debanne, D., Gähwiler, B.H. and Thompson, S.M. (1996) *Proc. Natl. Acad. Sci. U. S. A.* 93, 11225–11230
- 115 Debanne, D. et al. (1996) *J. Physiol.* 491, 163–176
- 116 Miles, R. (1990) *J. Physiol.* 431, 659–676
- 117 Thompson, S.M. et al. (1996) *J. Comp. Neurol.* 372, 515–528
- 118 Drake, A. et al. (1996) *Neuroscience* 70, 31–45
- 119 Schiavo, G. et al. (1995) in *Clostridial Neurotoxins* (Montecucco, C., ed.), pp. 257–274, Springer
- 120 Söllner, T. et al. (1993) *Nature* 362, 318–324
- 121 Williamson, L.C. et al. (1996) *J. Biol. Chem.* 271, 7694–7699
- 122 Gillis, K.D., Mössner, R. and Neher, E. (1996) *Neuron* 16, 1209–1220

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Neural transplantation studies reveal the brain's capacity for continuous reconstruction

Ole Isacson and Terrence Deacon

Basic research using cell transplantation indicates that structural developmental mechanisms seen in immature brains can also function in the adult brain. As the brain matures, cellular migration and axonal growth is impeded. However, fetal neural transplantation studies have shown that directional cues are available for fetal axons to find specific host neurons in the adult brain. By reaching specific and distant CNS target zones, donor tissue with extended axonal growth periods demonstrate both an abundance and specificity of CNS neurotropic signals. The presence of specific guidance cues, despite strong inhibition of regenerative long-distance axonal growth, suggests that these cues play other physiological roles in the adult CNS, and could be utilized therapeutically for reconnection of neuronal pathways.

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IN 1985, Floeter and Jones¹ showed that axons from embryonic cortical neurons implanted into newborn rat brain (postnatal day 0; P0) grew extensively towards the opposite cerebral hemisphere, the ipsilateral thalamus and the spinal cord: normal targets for the sensory motor cortex. These engrafted cells (pre-labeled with radioactive thymidine) also connected

with afferent fibers from host cortical and thalamic neurons. In parallel work in the developing cerebral cortex, Stanfield and O'Leary² showed that transplanted fetal neurons sought out the same targets (also transient) as during normal development. Zimmer and colleagues³ showed that embryonic hippocampus implanted into P0–P5 neonatal hosts

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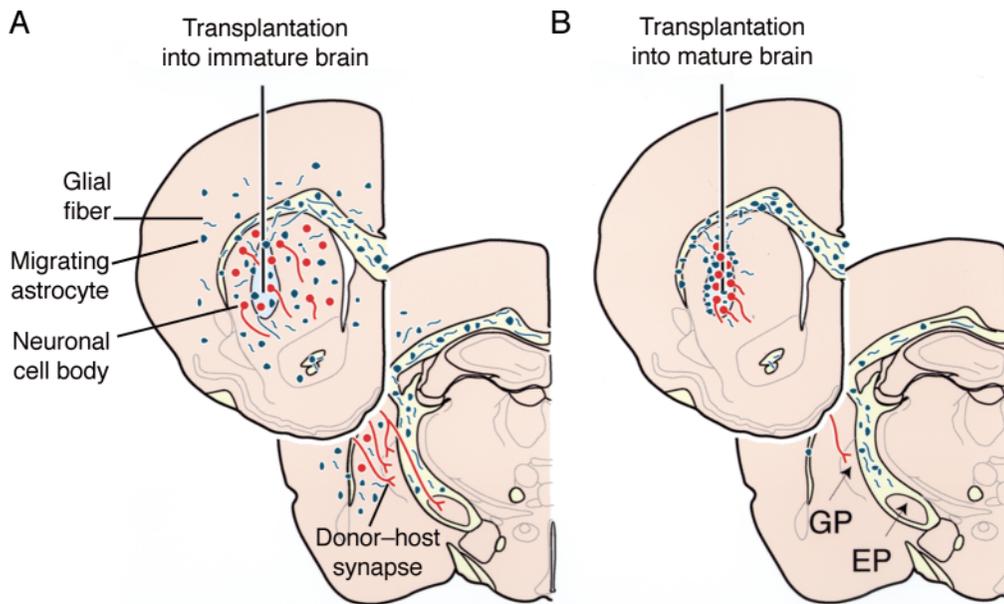


Fig. 1. Integration and growth of axons in fetal neural cells – immature vs mature brains. (A) Transplantation into immature brains results in extensive migration of both donor neurons (red) and glia (green). Neuronal cell bodies implanted in heterotopic sites (here illustrated by fetal ganglionic eminence cells implanted into the caudate–putamen)^{4–6} in an immature brain can migrate some distance, where transplanted cells appear to integrate in an organotypic fashion with host cells. Axonal growth is also appropriately target directed. In addition, glial cells migrate from the implantation site, although in immature brains they do not appear to exhibit any obvious target tropism (left panel). (B) By contrast, when implanted into mature brains, fetal neurons (red) and glia (green) can exhibit strikingly different mobility. Implanted neurons reaggregate and do not leave the immediate vicinity of the implantation site. Using histological techniques, axons and glia can be observed to grow out of the graft and into adjacent tissues in the mature host brain^{9,10}. Longer donor axonal growth can be achieved in the adult brain by manipulating the choice of fetal donor species (see Fig. 2). Abbreviations: EP, entopeduncular nucleus; GP, globus pallidus.

formed appropriate connections (afferent and efferent) with the host brain. However, these investigators also found that as the age of the host increased beyond the neonatal stage, migration of the implanted embryonic donor cells decreased, outgrowth from the grafted cells was reduced and synaptic contacts from the host were fewer³. When transplanted into neonates, fetal axons reach distant host targets^{1,3,6} that they seldom reach in adult brains. Several of these observations have been confirmed in other neural transplantation paradigms^{4–6}, revealing that implanted embryonic cells placed into immature brain (up to or before P7) will migrate and integrate, whereas in adult brain this rarely happens^{4,5}. These results are consistent with the view that in mammals, axonal growth is confined to the prepubertal phase, and that as brains mature and there is less axonal trophic support, molecules inhibitory to axonal growth are abundant^{7,8}. Thus, these inhibitory conditions would set limits on the structural flexibility of the adult CNS. The extracellular matrix of immature brains might provide more-permissive substrates for rapid axon growth than adult brain; however, the relative contribution of reduced adhesive substrates compared with increased inhibitory signals for axonal growth in the adult brain is difficult to determine (Fig. 1).

In some cases, local migration of fetal neurons is possible in the adult brain. In a model of selective, photolytically induced, cortical neuronal loss, Hermit-Grant and Macklis¹¹ showed that transplanted, neocortical (day 17) neuroblasts can migrate to their normal cortical laminar positions, differentiate appropriately and grow connections to a number of target sites. This type of neuroblast migration into the

neocortex is consistent with earlier findings by Sotelo and Alvarado-Mallart¹². In a mutant mouse strain lacking cerebellar Purkinje cells, they demonstrated that transplanted fetal cerebellar neurons could replace these missing cells. This indicates that the adult brain can be permissive for differentiation and structural integration of committed fetal neural cells. However, these authors did not find any axonal projections from the implanted Purkinje cells, such as towards deep cerebellar nuclei¹². Although immature cells are more restricted in mobility and in the ability to grow axons to distant targets in adult brains, there is now growing evidence that the adult host brain retains the capacity to guide growing fetal axons towards normal target neurons.

Directional cues for fetal axons to find specific host neurons in the adult brain

Cell transplantation into the mature brain indicates that axonal growth from embryonic neurons is highly target directed; a feature previously considered unique to the immature brains. A large number of experiments show that adult neurotropic signaling can be appropriately interpreted by immature neurons.

Observations of specific patterned axonal outgrowth from distinct phenotypes of neurons with similar neurotransmitter characteristics have been made in transplantation experiments involving the dopaminergic nigro–striatal system. Cells transplanted from the fetal ventral mesencephalon (VM) include many cell types and classes of neurons, and at least two subsets of dopamine (DA) neurons, each of which exhibits distinct connections with forebrain targets. For instance, the developing substantia nigra pars compacta (SN; area A9 in the adult) contains neurons that have overlapping, but distinct axonal target zones in the striatum compared with DA neurons in the medial VM (area A10) (Fig. 2A). Schultzberg *et al.*¹³ observed that in solid fetal VM transplants placed ectopically above the striatum, A10 DA neurons [also expressing the cholecystokinin (CCK) neuropeptide] grew into neocortex but did not grow into the dorsal striatum (A9 target zone) as was observed for transplant-derived CCK[−] DA fibers (Fig. 2C). Foster *et al.*¹⁵ provided early data demonstrating that serotonergic neurons from distinct fetal brain-stem nuclei grew in different trajectories when placed in adult striatum, hippocampus or spinal cord¹⁵. We have also addressed the question of axonal growth specificity of the mesencephalic DA system by characterizing axonal outgrowth patterns of a group of aldehyde dehydrogenase (ADH⁺) DA neurons (~30–40% of all DA neurons in the VM) after transplantation into the adult rat striatum¹⁴. We find that fetal DA neurons coexpressing ADH innervate the motor regions of dorsal striatum, which is also seen in the normal development of the brain (Fig. 2B). This could be interpreted

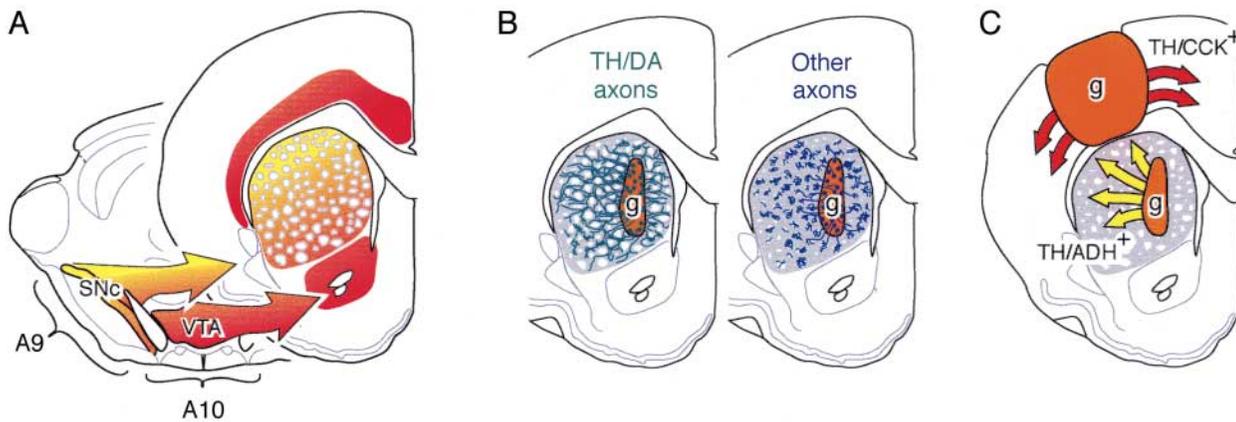


Fig. 2. Patterns of axonal growth from transplantation of different phenotypes of neurons in the adult brain. (A) Diagram of the normal innervation pattern of dopamine (DA) axons within the forebrain. Two features are exemplified by color coding: a tendency for DA fibers to avoid striatal white matter fiber bundles to terminate in striatal gray matter; and a difference in target-directed growth to the forebrain from different subpopulations of DA neurons. Substantia nigra pars compacta (SNc, A9; yellow) contains DA neurons that project predominantly to dorsolateral striatum. The ventral tegmental area (VTA, A10; red) project DA axons predominantly to ventromedial striatum, nucleus accumbens, neocortex and limbic structures. Some DA-containing neurons of the SNc also express the enzyme aldehyde dehydrogenase (ADH; yellow) and extend axons into more-dorsal and lateral divisions of the striatum. By contrast, most DA-containing neurons of the medial ventral mesencephalon (VM; A10 region) also express the cholecystokinin (CCK; red) neuropeptide and can extend axons into the neocortex. (B) When fetal VM cells are grafted (g) to the striatal host target region, their axons grow in patterns that reflect differences in neuronal DA phenotypes. DA axons growing out from fetal VM grafts (green) ramify exclusively in the host striatal gray matter, their normal target tissue, whereas non-DA axons (blue) from these grafts extend into host myelinated fiber bundles. (C) Target specificity of these DA cell types is demonstrated by different patterns of outgrowth of axons expressing either tyrosine hydroxylase (TH)⁺/ADH⁺ (yellow) or TH/CCK⁺ (red) from VM grafts placed either in striatum¹⁴ or cortex¹³.

as a possible target-induction of the ADH⁺ DA phenotype after connection to the adult striatum; however, a mechanism more consistent with normal development is that the ADH⁺ DA neurons are specified at the time of transplantation (E16) to grow towards this specific striatal target zone^{14,16}. Such specificity of axonal growth is also demonstrated by differences in axonal growth from DA and non-DA neurons present in VM grafts in the striatum (Fig. 2B). DA axons from fetal xenogeneic VM grafts ramify exclusively in the striatal gray matter, their normal target tissue. However, axons from non-catecholaminergic neurons avoid the adjacent gray matter and instead form trajectories exclusively towards nonstriatal gray matter target regions, via myelinated fiber bundles^{9,10}. Such phenotypic specializations indicate that these specific CNS fetal neuronal phenotypes are committed to selectively seek out target contacts, and recent data in other model systems (see Fig. 3) also indicate that the adult brain provides highly specific information for growing axons to find their appropriate targets¹⁰.

Other examples of local specificity of new axonal growth in the adult brain have come from experiments using fetal cholinergic neurons from different anatomical origins, allotransplanted ectopically into cortical brain areas where cholinergic axons normally branch and synapse. In a series of experiments, Nilsson and colleagues^{17,18} implanted cholinergic fetal cells derived from the fetal septum, nucleus basalis, striatum or the spinal cord; at a time just before axonal target selection in the developing brain, such cholinergic fetal cells were implanted into adult hippocampus that had been denervated of its normal afferent cholinergic fibers. In normal brains, these neurochemically similar neurons from different fetal brain regions would have grown axons and synapsed in distinct targets. These experiments showed that the fetal septum was the only cholinergic cell source that extended a normal pattern of dense cholinergic fiber outgrowth into the hilus and the supergranular band

of the dentate gyrus, and the hippocampus pyramidal cell laminae CA3 and CA1. By contrast, fetal cholinergic neurons derived from the nucleus basalis, which do not normally grow axons in the hippocampus, produced less cholinergic axonal outgrowth to the dentate gyrus. Placing cholinergic neurons from the fetal striatum into the hippocampus also produced very sparse cholinergic outgrowth. Finally, fetal cholinergic neurons derived from brainstem created a different axonal outgrowth pattern than the other fetal cholinergic cell sources^{17,18}. In summary, these studies indicate that the formation of new cholinergic connections in the hippocampus is a selective and regulated process in which phenotypic neuronal characteristics other than the neurotransmitter type are operational. In a complementary study, Dunnett *et al.*¹⁹ found that fetal cholinergic neurons from nucleus basalis tissue produced a significantly larger axonal cholinergic outgrowth into the adult neocortex than did fetal cholinergic neurons from the septum. In addition, neural xenotransplantation experiments illustrate that axonal orientation stimuli in the adult brain are sufficiently strong to direct growing fetal axons towards appropriate targets even through atypical anatomical pathways, and despite denervation lesions of inappropriate targets¹⁰.

Fetal neural xenotransplantation in the adult brain

In the mature brain, the range of axon guidance factors present is difficult to study as host regeneration is minimal and long-distance axonal growth from fetal neural allografts is usually limited (see Fig. 1). However, using donor tissue from relatively larger, slower maturing species, we and others have found that highly directed, long-distance axonal growth is possible^{9,10,20–22}. For example, when immature neurons with protracted development (such as from human or pig embryos) are implanted into adult animal hosts with relatively small brains (such as rats) the relatively longer time window of development of these donor

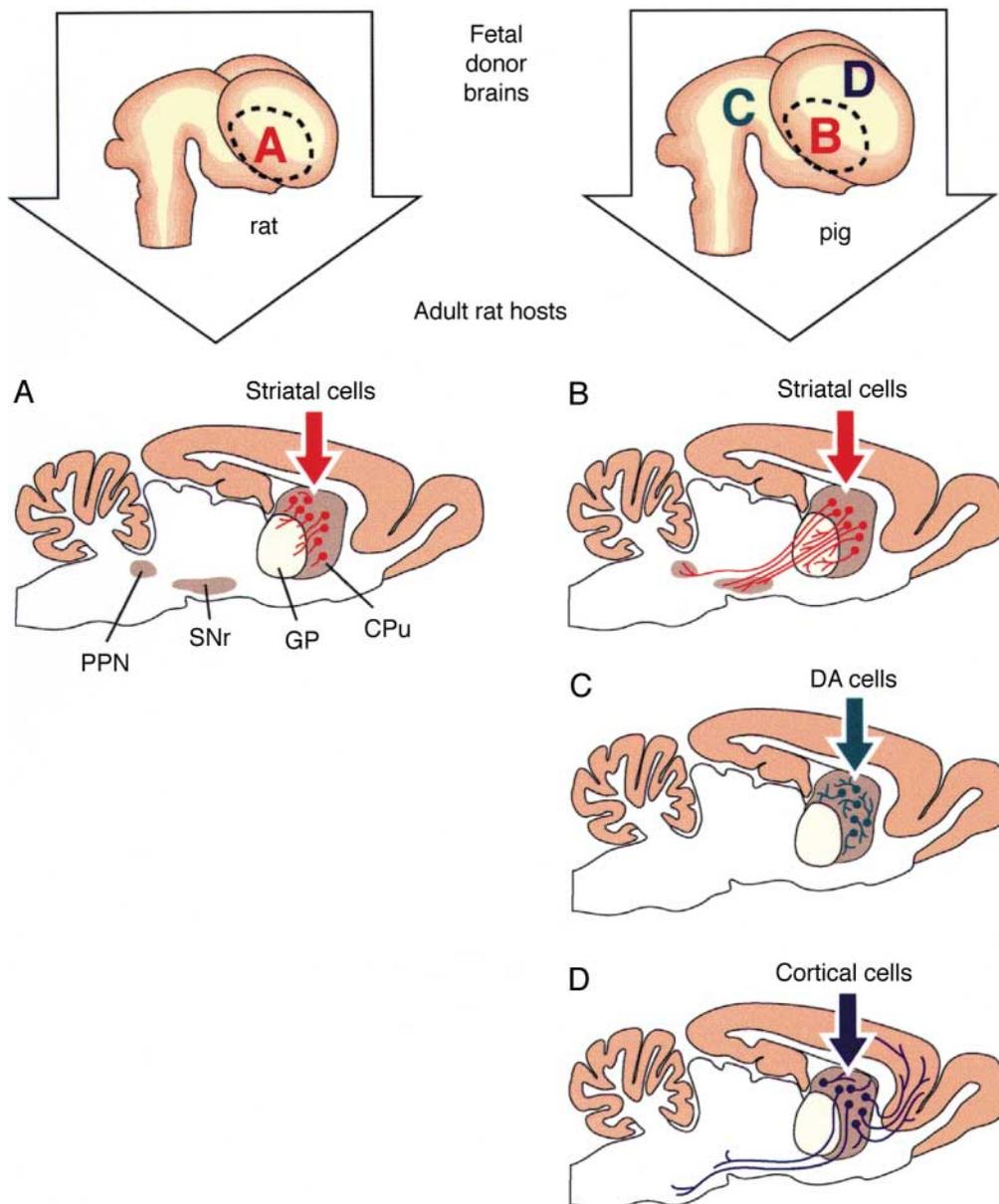


Fig. 3. Specificity of new axonal growth in the adult brain. By using fetal neural cells from a xenogeneic donor species that is considerably larger than the host species, it is possible to take advantage of the significantly prolonged maturation of the donor cells to grow axons over long distances despite the slow axonal growth that results from host inhibitory influences (see text). This makes it possible to unmask the presence of tropic signals and axon-growth-selective substrates in adult brains that have not previously been recognized. (A) Transplanted neurons from fetal rat striatal primordium grow axons primarily to local targets (<3 mm). By contrast, transplanted neurons from human and pig fetal striatum can grow axons to target structures at least 10 mm away from the implantation site. We implanted donor cells that were selectively dissected from different regions of the fetal pig brain and implanted them into both homotopic and heterotopic host brain regions to test for differences in growth and signaling characteristics^{9,10}. (B), (C) and (D) depict the axonal growth differences between donor striatal neurons (B), donor ventral mesencephalon (VM; dopaminergic) neurons (C), and donor lateral cerebral cortical neurons (D) implanted into the same site (striatum) in an adult rat brain. Each committed donor cell type extended axons along distinctive trajectories towards targets that were appropriate for their anatomical sites of origin. Striatal graft axons selectively innervated the globus pallidus (GP), entopeduncular nucleus (not shown), substantia nigra (SNr) and pedunculopontine nucleus (PPN); B); VM graft dopaminergic axons project only to surrounding striatal gray matter (C); and cortical graft axons extend to the cerebral cortex, the surrounding striatum and through the internal capsule to the cerebral peduncle (D). These distinctive axonal growth patterns indicate that some appropriate guidance cues are provided to these growing axons by the host brain, and demonstrate that these cues are functionally conserved across the rat–pig species difference. Abbreviation: CPu, caudate–putamen.

longer period to establish significant innervation of distant targets, than in the fetal or neonatal brain^{10,22}. One alternative hypothesis is that rather than just extending the time of growth, xenogenic neurons would not respond fully to inhibitory signals in host gray or white matter. We think this is possible, but a less plausible explanation, because we find that growth of xenogeneic axons in the adult is relatively impeded compared with growth in the developing (<P7) brain, indicating that growth inhibition seen in syngeneic transplant conditions is also present in xenogenic settings. Furthermore, the trajectories chosen towards appropriate targets are most consistent with an interpretation predicting a presence of diffusible chemoattractants and repellants of ingrowth into inappropriate gray matter zones¹⁰. Recent data by Chen *et al.*²³ obtained from transgenic mice overexpressing Bcl2 are also consistent with this view of the adult brain's structural plasticity. Their results from the lesioned retino–tectal systems indicate that an increased time for axonal extension is associated with enhanced capacity for long-distance regeneration, in a highly target-specific manner²³. Therefore, any intervention that will keep axons in active growth would enhance therapies aimed at CNS neural repair and regeneration, even in the adult. Taken together, fetal neuronal transplantation results show that despite the relatively nonpermissive substrates for axonal growth and cell migration within the adult brain, cues for axonal guidance are available for appropriate reconstruction. In addition, the considerable distance over which these axon guidance cues work suggests that directional signals are both widespread and abundant in the adult brain (see Fig. 3).

The mechanisms by which fetal axonal-growth-cones can reach targets, despite the presence of nonpermissive substrates in the adult brain, might be related to growth-cone guidance in the developing brain^{24,25}. In normal development, axonal growth occurs in spurts of growth interrupted by growth cone collapse^{8,24,26}. It appears that mol-

neurons appears to enable their axons to reach distant targets^{9,10,20,21}. Moreover, results from these xenotransplantation experiments suggest that target selection and patterns of axonal growth are similar between immature and mature brains. Notably, this axonal growth in adult host brain requires a considerably

ecular gradients of attractive and inhibitory cues provide orientation towards correct targets by inducing asymmetric growth-cone collapse and extension^{27,28}. Axons from transplanted fetal neurons can reach their correct destinations when transplanted into the adult brain, even from ectopic locations (see Fig. 3C,D), but

the rate at which the axons reach (or can remain) at their targets appears much lower than in the developing immature CNS (Ref. 10). This suggests that in fetal neuronal growth both fetal allo- and xenogeneic axon-growth-cones are inhibited in their rate of growth by the adult CNS substrate and only reach distant targets by persisting in a growing state for longer than normal.

The directed and selective axonal growth of implanted fetal neurons implies that the mature brain continues to express a large number of structural tropic signals also in regions where synaptic connections are fully established^{9,10}. Assuming that there is continuous structural remodeling at the synaptic level^{29,30}, the pronounced inhibition of long-distance regenerative axon growth in the adult CNS might normally function to limit axon growth away from appropriate targets, and conversely limit ingrowth from inappropriate neurons. These features might have evolved to allow structural plasticity while restricting aberrant axonal growth, thereby stabilizing functional domains in the normal adult brain.

Functional recovery depends on characteristics of the transplanted cells and interactions with the host brain

Some of the observed fidelity in anatomical and cellular specificity might not be an absolute requirement for functional repair of the CNS. Behavioral experiments show that fetal neural grafts that contain cholinergic neurons, when placed in the hippocampus, can reverse alcohol-induced deficits in radial maze performance, independent of their fetal origin and cholinergic phenotype, whereas non-cholinergic grafts had no beneficial effect³¹. Thus, precise anatomical reconstruction of neuronal circuitry might not be required for some functional effects to occur, perhaps because of the plasticity of the adult host brain and its adaptation to the functional development of transplanted cells. For example, Mayer *et al.*³² showed that at a time when all axons from neurons grafted from the fetal striatum had probably reached their host targets, the behavioral recovery continued. They interpreted their finding as evidence for 'learning to use the transplant' by the host. Xenotransplantation studies also provide evidence for factors influencing the timing of developmental events. Experiments using committed fetal neural cells indicate that these cells will develop in the host according to a schedule of growth and differentiation appropriate to the species of origin. Fetal neural cells and xenografts from embryonic striatum or VM will develop organotypically and express the neuronal phenotypes seen in the adult striatum or VM^{9,21,22,33,34}. A remarkable example of the donor-specific schedule of development comes from behavioral experiments in a rat model of Parkinson's disease using implantation of cells from different donor species with different developmental time-courses. In these cases, behavioral recovery corresponded to the donor-specific rate of neuronal and synaptic maturation (Fig. 4). Recovery of dopaminergic function due to graft maturation within the striatum, including maturation of new synapses is correlated with decrease of this rotational asymmetry. A meta-analysis of studies performed (by different research teams), shows that mouse³⁵, pig³³ and human³⁶ fetal ventral mesencephalon xenotransplanted into PD rats can ameliorate rotational asym-

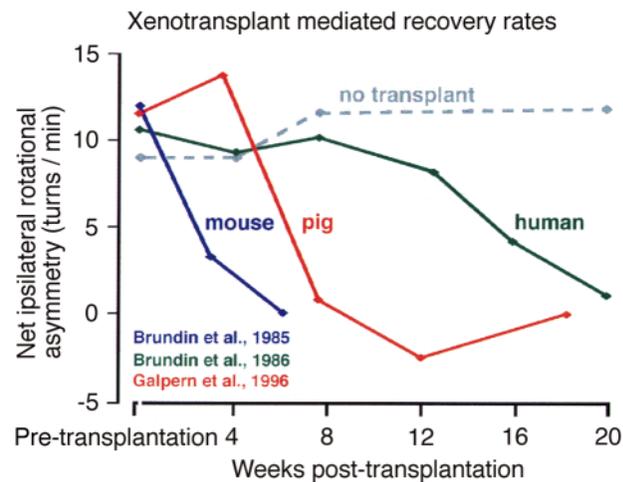


Fig. 4. Xenotransplantation of fetal DA cells in a Parkinson's disease (PD) model in rats has made it possible to directly compare the timing of functional development of grafted cells from different donor species. The DA neurons and fibers from the substantia nigra pars compacta on one side of the rat brain are chemically lesioned using injections of the selective catecholaminergic neurotoxin 6-hydroxydopamine; this significantly depletes the dopaminergic input to the ipsilateral striatum. Consequently the rat exhibits a strong locomotor bias contralateral to the side of the intact striatum. This can be exaggerated by pharmacological administration of amphetamine (a dopamine releasing agent), providing a robust behavioral assay of the difference in dopaminergic function on the two sides of the brain. Comparing the rate of behavioral recovery reveals differences consistent with the donor's relative rate of neural maturation (see text for details).

metry. Comparing the rate of behavioral recovery (reduction in asymmetry), reveals differences consistent with the donor species' comparative rates of neural maturation. Mouse donor cells produce the most rapid recovery³⁵, human cells produce the most protracted recovery³⁶, and porcine cells produce an intermediate rate³³. Differences in axonal growth rates are unlikely to be the major contributing factor to this difference in recovery rates as the distances from graft to host target cells are small in the striatum due to their heterotopic implantation. Furthermore, tyrosine hydroxylase activity is present in donor cells at early stages of graft maturation, before behavioral recovery, and presumably correlates with dopamine production^{37,38}. Therefore, we hypothesize that donor synapse maturation is the major determining factor contributing to this difference in onset of function in this particular model.

Concluding remarks

Transplantation studies utilizing fetal neural cells demonstrate that although support for differentiation, cell migration and axonal growth are progressively reduced during CNS maturation, signaling mechanisms sufficient to support these developmental processes persist in adult brains and can be utilized by transplanted immature cells. Thus, the overriding inhibition of regenerative long-distance axonal growth seen in the adult CNS might co-exist with an abundance of axon guidance cues, that may also play other physiological roles in the adult CNS (Ref. 9). These findings might help us understand the fundamental principles of structure and process plasticity of the CNS as well as its capacity to be repaired after damage.

Selected references

- 1 Jones, E.G. and Floeter, M.K. (1985) in *Neural Grafting in the Mammalian CNS* (Björklund, A. and Stenevi, U., eds), Elsevier
- 2 Stanfield, B.B. and O'Leary, D.D. (1985) *Nature* 313, 135–137
- 3 Zimmer, J. *et al.* (1985) in *Neural Grafting in the Mammalian CNS* (Björklund, A. and Stenevi, U., eds), Elsevier
- 4 Campbell, K., Olsson, M. and Björklund, A. (1995) *Neuron* 15, 1259–1273
- 5 Brüstle, O., Maskos, U. and McKay, R.D.G. (1995) *Neuron* 15, 1275–1285
- 6 Victorin, K. *et al.* (1996) *Soc. Neurosci. Abstr.* 1491
- 7 Schwab, M.E. and Caroni, P. (1988) *J. Neurosci.* 8, 2381–2393
- 8 Patterson, P.H. (1988) *Neuron* 1, 263–267
- 9 Isacson, O. *et al.* (1995) *Nat. Med.* 1, 1189–1194
- 10 Isacson, O. and Deacon, T. (1996) *Neuroscience* 75, 827–837
- 11 Hernit-Grant, C.S. and Macklis, J.D. (1996) *Exp. Neurol.* 139, 131–142
- 12 Sotelo, C. and Alvarado-Mallart, R.M. (1987) *Nature* 327, 421–423
- 13 Schultzberg, M. *et al.* (1984) *Neuroscience* 12, 17–32
- 14 Haque, N.S.K., LeBlanc, C.J. and Isacson, O. (1997) *Cell Transplant.* 6, 239–248
- 15 Foster, G.A. *et al.* (1988) *Exp. Brain Res.* 70, 242–255
- 16 McCaffery, P. and Drager, U.C. (1994) *Proc. Natl. Acad. Sci. U. S. A.* 91, 7772–7776
- 17 Nilsson, O.G. *et al.* (1988) *J. Comp. Neurol.* 268, 204–222
- 18 Nilsson, O.G. *et al.* (1988) *Brain Res.* 456, 193–198
- 19 Dunnett, S.B. *et al.* (1986) *Brain Res.* 378, 357–373
- 20 Victorin, K. *et al.* (1990) *Nature* 347, 556–558
- 21 Victorin, K. *et al.* (1992) *J. Comp. Neurol.* 323, 475–494
- 22 Deacon, T.W. *et al.* (1994) *Exp. Neurol.* 130, 151–167
- 23 Chen, D.F. *et al.* (1997) *Nature* 385, 434–439
- 24 Stirling, R.V. and Dunlop, S.A. (1995) *Trends Neurosci.* 18, 111–115
- 25 Molnár, Z. and Blakemore, C. (1995) *Trends Neurosci.* 18, 389–397
- 26 Keynes, R.J. and Cook, G.M.W. (1992) *Curr. Opin. Neurobiol.* 2, 55–59
- 27 Colamarino, S.A. and Tessier-Lavigne, M. (1995) *Cell* 81, 621–629
- 28 Richards, L.J. *et al.* (1997) *J. Neurosci.* 17, 2445–2458
- 29 Lo, D.C. (1995) *Neuron* 15, 979–981
- 30 Franklin, R.J. and Blakemore, W.F. (1995) *Trends Neurosci.* 18, 151–156
- 31 Hodges, H. *et al.* (1991) *Behav. Brain Res.* 43, 7–28
- 32 Mayer, E. *et al.* (1992) *Eur. J. Neurosci.* 4, 119–126
- 33 Galpern, W.R. *et al.* (1996) *Exp. Neurol.* 140, 1–13
- 34 Olanow, C.W., Kordower, J.H. and Freeman, T.B. (1996) *Trends Neurosci.* 19, 102–109
- 35 Brundin, P. *et al.* (1985) *Exp. Brain Res.* 60, 204–208
- 36 Brundin, P. *et al.* (1986) *Exp. Brain Res.* 65, 235–240
- 37 Clarke, D.J. *et al.* (1988) *Exp. Brain Res.* 73, 115–126
- 38 Freeman, T.B. *et al.* (1988) *Prog. Brain Res.* 78, 473–477

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Adenosine–dopamine receptor–receptor interactions as an integrative mechanism in the basal ganglia

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Increasing evidence suggests that antagonistic interactions between specific subtypes of adenosine and dopamine receptors in the basal ganglia are involved in the motor depressant effects of adenosine receptor agonists and the motor stimulant effects of adenosine receptor antagonists, such as caffeine. The GABAergic striatopallidal neurons are regulated by interacting adenosine A_{2A} and dopamine D₂ receptors. On the other hand, the GABAergic striatonigral and striatoentopeduncular neurons seem to be regulated by interacting adenosine A₁ and dopamine D₁ receptors. Furthermore, behavioural studies have revealed interactions between adenosine A_{2A} and dopamine D₁ receptors that occur at the network level. These adenosine–dopamine receptor–receptor interactions might offer new therapeutic leads for basal ganglia disorders.

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DOPAMINERGIC NEUROTRANSMISSION is involved in the motor depressant effects of adenosine-receptor agonists and in the motor stimulating effects of adenosine-receptor antagonists, such as caffeine, the most consumed psychoactive drug in the world. The motor activation induced by adenosine-receptor antagonists is counteracted by treatments that cause an acute dopamine depletion or dopamine-receptor blockade¹. Furthermore, adenosine-receptor agonists inhibit and adenosine-receptor antagonists potentiate the motor activating effects of dopamine-receptor agonists¹. Specific interactions between specific subtypes of adenosine and dopamine receptor in the basal ganglia are involved in this antagonistic interaction between the neuromodulator adenosine and the neurotransmitter dopamine.

Localization of dopamine and adenosine receptors in the basal ganglia

The striatum (morphologically divided into caudate–putamen, nucleus accumbens and olfactory tubercle) receives glutamatergic inputs from cortical, cortical-like and thalamic areas^{2,3}. Most striatal neurons (more than 90%) are GABAergic medium-sized spiny neurons and the second most abundant striatal neuron is the large cholinergic aspiny interneuron (about 5%). There are two subtypes of striatal GABAergic efferent neurons: striatopallidal neurons, which contain the peptide enkephalin and connect the striatum with the pallidal complex (globus pallidus and ventral pallidum); and striatonigral and striato–entopeduncular neurons, which contain the peptides substance P and dynorphin. These