Graft-Induced Recovery of Cognitive Function
After Diffuse or Focal Brain Damage

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Recent neuroimaging techniques have linked amnesia to focal hippocampal damage following reduced cerebral blood flow during heart attack /4/, whereas cognitive deficits in Alzheimer's disease are associated with widespread neurodegeneration, notably in cholinergic projections. As a model for aspects of diffuse neurodegenerative damage we have employed excitotoxic lesions of the nucleus basalis and medial septal areas /1/, at the source of cholinergic projections to cortex and hippocampus, and chronic alcohol treatment /2/ (20% v/v in drinking water for 28 weeks), both of which resulted in long-lasting deficits in 8-arm radial maze performance, and reductions in cortical and hippocampal choline acetyltransferase (Chat) activity. Lesioned and alcohol-treated animals also showed bi-directional sensitivity to cholinergic drugs, exhibiting further impairment in response to antagonists (scopolamine and mecamylamine) and improvements with agonists (arecoline and nicotine) at low doses which did not affect the performance of controls. In both groups ectopic grafts within the terminal areas (cortex and/or hippocampus) of foetal cholinergic-rich basal forebrain tissue, dissected at embryonic day 15 (E 15), promoted functional recovery. Cholinergic-poor grafts of E 18 hippocampal tissue were without effect, as were basal forebrain grafts sited within the lesioned host basal forebrain. Alcohol-treated animals also showed recovery following non-organotypic cholinergic-rich E 14 pontine grafts, and lesioned rats with cell line IMR 32 /3/ and NS 20Y grafts derived from human neuroblastomas. Error rates in lesioned rats with IMR 32 and NS 20Y grafts increased after experimental graft rejection, suggesting that functional recovery depended on the continuing presence of the graft.

As a model of focal anoxic damage we have demonstrated deficits in spatial learning in the water maze in rats with 90% loss of dorsal CA1 cells following transient forebrain ischaemia induced by electrocauterisation of the vertebral arteries, followed 24 h later by ligation of the carotid arteries for 15 min (4 vessel occlusion: 4 VO). Ischaemic deficits included increased latency to find a hidden platform, decreased time spent in the training quadrant and increased time spent searching close to the platform, indicating impairment both in search strategy and localization. In ischaemic rats E 18-19 grafts dissected from the CA1 subfield, placed homotypically adjacent to the area of CA1 cell loss improved spatial navigation. Heterotypic E 18-19 CA3 grafts, dentate granule (DG) cells dissected either E 18-19 or post natal day 1-2, and E 15 basal forebrain grafts all failed to improve spatial learning. Effects of grafts appeared to be subfield-specific, as in animals with colchicine lesions of the dentate gyrus which also showed impaired spatial navigation, DG, but not CA1, grafts promoted functional recovery. Since both DG and CA1 cells are glutamatergic, these findings suggested that homotypic grafts were required, rather than cells releasing an appropriate transmitter.

The findings suggested that foetal grafts promote functional recovery both after damage to the diffusely projecting cholinergic system and after focal damage within the hippocampus, but that the mechanisms might differ. Firstly, ectopic grafts in the terminal fields were effective in animals with cholinergic depletion, grafts in the basal forebrain lesion sites were ineffective, and
rats with hippocampal damage showed recovery with grafts adjacent to the areas of cell loss. Secondly, cholinergic deficient rats showed improvement following implantation with several different types of cells with cholinergic properties, including cell lines, foetal basal forebrain, and pontine tissue. In contrast, rats with hippocampal damage showed improvement only with appropriate subfield grafts; cells from proximal fields of similar morphology and/or transmitter content were ineffective. Since lesioned and alcohol-treated animals were responsive to cholinergic agonists, the findings suggested that graft-induced functional recovery following cholinergic model involves non-specific synaptic links, and/or diffusion of neurotransmitters or growth factors related to acetylcholine. However, the more stringent requirements after selective loss of cells within a hippocampal field suggests that grafts may serve to reconstruct or bridge the damaged circuit. As visualized by Nissl, Timm and acetylcholinesterase staining, CA1 grafts were of appropriate morphology, sited above damaged host CA1 area and in receipt of host septal innervation, but a detailed study of graft-host connectivity is required to ascertain how far these grafts establish point-to-point links with the ischaemic host brain.

REFERENCES
