Recovery recapitulates ontogeny

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Several studies support the hypothesis that after stroke, specific features of brain function revert to those seen at an early stage of development, with the subsequent process of recovery recapitulating ontogeny in many ways. Many clinical characteristics of stroke recovery resemble normal development, particularly in the motor system. Consistent with this, brain-mapping studies after an ischemic insult suggest re-emergence of childhood organizational patterns: recovery being associated with a return to adult patterns. Experimental animal studies demonstrate increased levels of developmental proteins, particularly in the area surrounding an infarct, suggesting an active process of reconditioning in response to cerebral ischemia. Understanding the patterns of similarity between normal development and stroke recovery might be of value in its treatment.

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STROKE remains the leading cause of adult disability in many Western countries, with survivors living with their deficits for an average of seven years[1]. In the weeks that follow a stroke, a number of changes take place in the brain. In many cases, these are associated with neurological improvement. The underpinnings of these restorative events have become the focus of intense study. In this article, aspects of stroke recovery that resemble normal development are reviewed. A better understanding of the analogies between development and recovery might be of value in the design of future studies, including formulation of therapeutic interventions that improve clinical outcome after stroke.

Most patients show some degree of recovery after a stroke, but few return to normal. Stroke recovery generally proceeds through a series of clinical stages[2,3]. In general, individuals with a larger extent of improvement proceed through a greater number of stages.

Motor performance

For several decades, researchers have described behavioral parallels between the successive stages of normal development and recovery from brain injury. For example, Hines showed that the normal development of locomotion and posture in rhesus monkeys passed through states similar to those seen during stroke recovery[4]. Teitelbaum *et al.* found that the four stages of feeding behavior in normal development re-emerged in rats recovering from a lateral hypothalamic injury[5]. Other studies from his laboratory determined that forelimb placing in the cat passed through the same stages during normal development and during recovery from a focal lesion[6]. More-recent studies in humans lend further support to such a link, especially with regard to motor function. In other cases, such as language, the case for a parallel between development and recovery might be less compelling.

A major theme common to both childhood development and successful recovery from hemiparetic stroke is the refinement in motor performance, from a gross movement to a fine, fractionated one. The sequence of events after stroke was well described by Twitchell[2]. Initially, activity depends on reflex responses. Primitive reflexes are disinhibited. The first volitional movements consist of whole-arm synergistic events, then proximal movements predominate. Movement of individual fingers appears later, as synkinesias resolve, and only when recovery is substantial. Slowness of fine finger movements is a cardinal sign of corticospinal tract damage; faster movements and shorter reaction times are seen as stroke recovery proceeds. This general pattern is similar to motor changes during normal development. Newborn infants respond in a generalized fashion to stimulation, with early responses showing much more movement of the entire upper extremity rather than of individual fingers[7]. Over time, movements become more precise and fractionated, with loss of synkinesias and inhibition of primitive reflexes. For example, the widely used Denver Developmental Screening Test[8] cites the median age for emergence of isolated thumb movements as three years. Children also show substantial improvement in motor speed during development[9].

What are the changes in brain function that underlie these improvements in motor function during stroke recovery, and how similar are they to the events of normal development? Brain-mapping studies have provided some insights, and a number of similarities have emerged, including those related to bilateral motor control and those related to plasticity of cortical representational maps.

Bilateral motor control

Childhood is associated with bilateral motor control, in association with immaturity of the corticospinal connections that are essential for fractionated unilateral movements. In contrast, adulthood is associated primarily with contralateral motor control, together with well-developed corticospinal tract size and function[10,11]. Muller *et al.*[12] found that transcranial magnetic stimulation of motor cortex induced bilateral responses in hand and arm muscles of most children, but only contralateral responses from the age of ten. The frequency with which ipsilateral responses were seen steadily decreased during the first decade of life. Another indication of bilateral control is the movement of both hands during intended use of only one, a phenomenon known as mirror movements. Mirror movements during hand motor tasks are normal in children, but decrease in their prevalence and magnitude, then disappear in the early teenage years[13]. There are very limited data that

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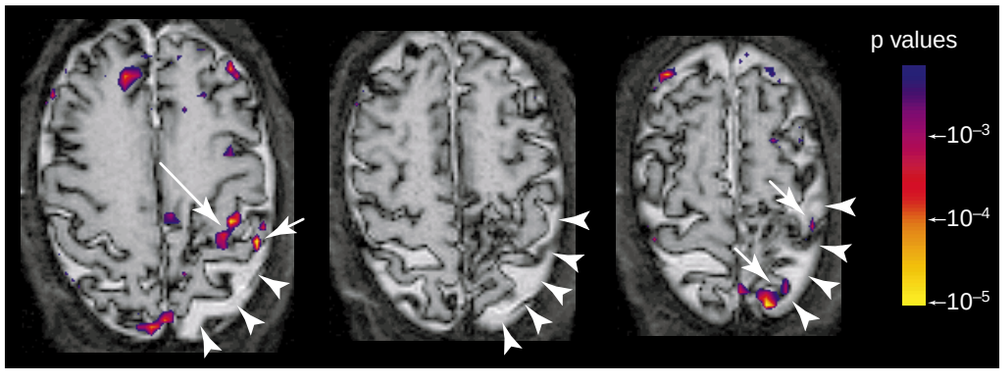

trends in Neurosciences

Fig. 1. ***Functional MRI study of a 75-year-old right-handed man imaged 3 months after an embolic stroke to the region of left primary sensorimotor cortex.*** *Imaging methods and finger-tapping results have been described previously[22]. Initially after the stroke, the right hand could make almost no movements. By the time of fMRI, his examination was normal. These images were obtained while he alternated between right hand squeezing (1 Hz, driven by a metronome) and rest. The three slices are sequential and 7 mm thick. The p values for significantly activated pixels (3.125 × 3.125 mm) are indicated by the color bar at right. The area of stroke is outlined by the arrowheads. There are two adjacent foci of activation along the left central sulcus, indicated by the long arrow. These are at the usual site for hand motor studies. In addition, three sites of peri-infarct activation are present, indicated by the short arrows.*

describe functional brain activation in children. Studies using near-infrared spectroscopy in normal infants have identified bilateral sensorimotor cortex activation during unilateral passive arm movements[14], in contrast to contralateral activation in response to the same movements in adults[15]. Gaillard *et al.*[16], using functional magnetic resonance imaging (fMRI) during a silent word-generation task, found that children activated a significantly larger volume of brain in the right hemisphere and in the right inferior frontal gyrus, when compared with adults.

Bilateral motor control has also been described in adults who have suffered a stroke. Neurophysiological features, however, suggest two different patterns. One is found in individuals with poor motor status, either soon after stroke or late after stroke in individuals with poor recovery. Neurophysiological evaluation of these individuals discloses features in common with children. A second pattern of bilateral motor control has been described in individuals with good recovery after stroke and has more similarities with the normal adult motor physiology.

Soon after stroke, and in individuals with poor recovery long after stroke, studies have demonstrated an increased degree of bilateral motor control that has similarities with normal childhood motor function. A PET study of six hemiplegic individuals early after stroke found bilaterally increased sensorimotor cortex activation during passive movement of the paretic arm, when compared with the same stimulus in controls[17]; this is the same stimulus that produced bilateral sensorimotor cortex activation in infants[14] and contralateral activation in healthy adults[15]. In the stroke hemisphere, soon after stroke and in individuals with poor recovery from stroke, there is often slowed central motor conduction time[18], a finding also seen in early childhood[12]. In the non-stroke hemisphere, transcranial magnetic stimulation (TMS) elicits motor responses in the ipsilateral (stroke-affected) hand, primarily in individuals with poor motor status[19,20]; such ipsilateral responses to TMS are seen in children but not in adults[12]. Furthermore, these ipsilateral responses to TMS among individuals who have not recovered from a stroke are delayed by several milliseconds compared with contralateral responses, similar to results in children[12]. As with motor behavior, neurophysiological characterization of individuals with poor motor status after stroke has a number of similarities with early stages of development.

Individuals with good recovery from a hemiparetic stroke also show increased bilateral motor control, however neurophysiological features are more consistent with findings in normal adults rather than a return to an early developmental pattern. PET and fMRI studies of individuals with good recovery after stroke have described bilateral activation in motor cortex regions during performance of a hand motor task[21–24]. In contrast to individuals with poor recovery, however, those who are well recovered have normal central motor conduction times[18] and fail to demonstrate ipsilateral motor responses during TMS of the non-stroke hemisphere (as do control subjects)[19,20]. Numerous studies have found that control subjects performing a unilateral motor task recruit ipsilateral motor cortex, though to a smaller extent than stroke subjects moving a recovered hand[21–24]. The site of ipsilateral motor cortex recruited by stroke and control subjects is similar. In controls, the sites activated in a given hemisphere during ipsilateral and during contralateral hand movements are spatially distinct. In the non-stroke hemisphere of stroke subjects, the site activated during ipsilateral (recovered) hand movement is separated from the site activated during contralateral (unaffected) movement. The pattern of separation in stroke is very similar to that seen in controls[25], suggesting that in stroke, a cortical region normally used for movement is being recruited, but in an exaggerated way.

The role played by motor cortex in its influence on ipsilateral hand movements can vary according to the pattern of bilateral control. In the first pattern, seen in children and in are individuals who have suffered a stroke without good recovery, ipsilateral control of hand movements has been considered a reflection of activity in undecussated corticospinal pathways[19,20]. The second pattern is seen in adults and in individuals with good recovery, suggesting that stroke recovery reflects reinstatement of motor control features that were acquired during development. In this group, ipsilateral control might reflect task complexity, as increasing the complexity of unilateral hand movements by normal adult subjects has been associated with greater activation of the ipsilateral motor cortex[26]. Alternatively, ipsilateral control might also be a function of motor suppression, as previous studies in primates (reviewed by Garol and Bucy[27]) and humans[28] have suggested the presence of a motor strip region related to suppressing contralateral movements of the distal upper extremity.

Cortical-map plasticity

Brain-mapping studies have supported the idea that in humans, a number of cortical regions contain orderly but overlapping representation of body regions[29,30]. In animal studies, these maps show a degree of redundancy

and overlap[31], a finding also described in human brain-mapping studies[32]. The capacity to reorganize cortical representational maps might be maximal at early time points in development. For example, hemispherectomy during early childhood can be associated with remapping of motor, language and other functions to regions within the remaining hemisphere[33,34].

Reorganization of cortical representational maps might also be a mechanism by which some individuals achieve return of function after stroke. Cortical-map plasticity is a normal event in adulthood and might be amplified after stroke. Studies in primates have demonstrated such plasticity along the rim of a focal infarct[35,36]. Brain-mapping studies suggest the same could be true in humans. For example, finger movements by individuals with good recovery from stroke have been associated with activation of motor-cortex regions traditionally associated with the face[21]. Functional imaging studies during finger movements[22,24] or exploratory hand movements[37] in individuals who have recovered from stroke have identified foci of activation along the edge of a cortical stroke (Fig. 1). These foci were not in motor-cortex regions generally associated with hand representation, suggesting that surviving regions along the infarct rim might be recruited in cortical-map reorganization. Multiple rearrangements can occur after a single stroke, and an improved understanding of cortical reorganization in this setting might come from studying patterns of change in multiple systems. For example, compared with controls, an individual recovered from a small precentral gyrus stroke showed a posterior shift in the activation site during both finger-motor and finger-sensory paradigms[38]. The total behavioral impact of these reorganizational events is difficult to know. Gains in one aspect of function might arise at the cost of another; for example, this might explain why stroke subjects often have mild motor deficits in the non-stroke hand in association with improvement in the stroke-affected hand[22].

There are a number of reasons to suspect that peri-infarct regions are a site of clinically relevant cortical remodeling. These regions have high levels of growth-related proteins (Table 1), and the volume of threatened but surviving peri-infarct tissue is linearly related to the degree of clinical recovery[39]. Animal studies are needed to determine the extent to which map reorganization corresponds to sites of increased growth-related protein levels. Studies in humans with a wide range in degree of recovery from stroke are needed in order to establish the specificity of map reorganization for the well-recovered state. Such studies might be useful in generating a non-invasive method for assessing restorative events as they occur during stroke recovery.

The cellular basis for brain recovery and reorganization has been studied in animal models of brain infarct. In many cases, changes are similar to events of normal development. Certainly, not all brain events that occur after stroke have a direct link with development, such as the inflammatory and excitotoxic events that follow an infarct. However, some processes that are seemingly unrelated to recovery, such as the inflammatory response, might serve in part as a trigger for restorative events[40]. Other processes in common are not specific for recovery and development. For example, the area surrounding an infarct shows a rapid increase in excitability and decrease in inhibition, findings that might contribute to LTP in the infarct surround[41].

TABLE 1. Proteins increased in brain during development and after ischemic insult

Type of protein	Name	Refs
Differentiation factor	NeuroD	81
Structural	Nestin	82,83
	MAP-2	84
Growth associated	GAP43	84,85
	Synaptophysin	53,85
Growth factors	Basic fibroblast growth factor	86
	Vascular endothelial growth factor	87
	Brain-derived neurotrophic factor	76
Cell cycle related	p53	
	p53 response proteins	88–90
	Cyclin D	84,91

Re-emergence of molecular and cellular developmental events

Developmental proteins normally absent or present at very low levels in adult brain re-emerge after an ischemic brain insult, often at a time of limited cellular metabolic resources. A wide range of proteins have been described, many focused in the penumbral area surrounding an infarct and some appearing in bilateral hemispheres (Fig. 2). Increased proteins levels after stroke are related to changes in the extracellular matrix, glial structure, neuronal growth, apoptosis, angiogenesis and cellular differentiation (Table 1). The production of many of these proteins also increases under other conditions, such as those related to memory and experience[42,43]. Re-emergence in adulthood of proteins normally associated with development is a pattern seen in many organ systems and indicates a conservation of plasticity mechanisms throughout the lifetime of an organism. For example, a similar pattern of reversion has also been described in the production of Ca^{2+} channels after myocardial infarction[44], growth factors in diabetes mellitus[45], developmental proteins after muscle fiber injury[46], and hemoglobin in myelodysplasia[47].

Cellular changes that are reminiscent of development arise in the setting of these molecular events. During brain development, the number of dendritic spines and synapses increases until several years after birth, with the numbers being reduced thereafter. In humans, for example, the number of synapses reaches a peak at age five[48]. In macaques, synaptic density peaks two months postnatally, being halved to reach adult levels at age three[49]. After a unilateral cortical lesion, increased dendritic branching[50,51] and an increased number of synapses[52,53] have been reported in both the stroke-affected and the non-stroke hemispheres. After an infarct some of these changes show an overshoot followed by pruning, as they do during development. There is also evidence, albeit incomplete, for quantitative changes in neurons after stroke. Recent data strongly support the presence of neurogenesis in healthy adult rodent[54] and primate brains[55]. A post-ischemic increase in production of cell-cycle proteins, including the neuronal determination protein neuroD (Table 1), suggests activation of neuronal stem and progenitor cells from a quiescent state. A recent study of mice showed that both endogenous subventricular cells and exogenously implanted bone-marrow cells proliferated, migrated, differentiated and were recruited to ischemic regions after embolic stroke[56].

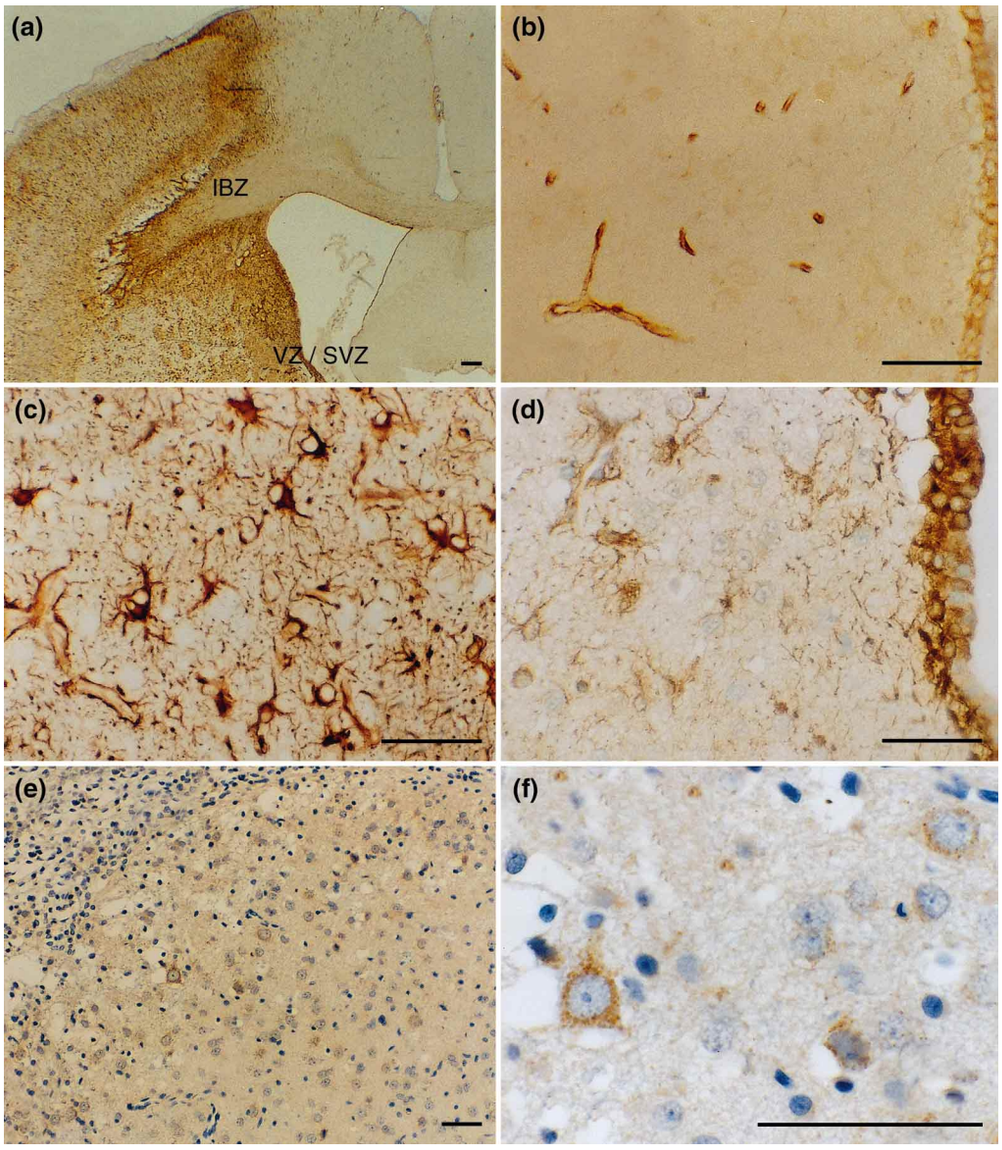

Fig. 2. ***Increased developmental proteins in the region surrounding an experimental infarct, seven days after a 2 h occlusion of the middle cerebral artery.*** **(a)–(d)** *show immunostaining for nestin. In non-ischemic brain regions, nestin immunoreactivity is present in endothelial cells and in the ventricular zone (VZ), for example, right side of* (a) *and* (b). *In the ischemic boundary zone [IBZ;* (c)*] and in the ventricular zone/subventricular zone [VZ/SVZ; see* (d)*], nestin immunoreactivity is increased.* **(e)** *and* **(f)** *show immunostaining for NeuroD. In* (e)*, NeuroD immunoreactivity is most intense in morphologically intact neurons in the IBZ. Note that* (f) *is enlarged from* (e). *Scale bar,100 μm.*

Many events after stroke resemble development, but what is the evidence that links patterns of cellular response with patterns of behavioral recovery? The answer to this question is central to the goal of using developmental events as a template for therapeutic approaches. Three pieces of evidence support this link.

There is a correlation between extent of behavioral recovery and magnitude of cellular response. This has been examined in studies that varied infarct site[51], level of motor activity[57,58] and chemical milieu[53,59]. For example, Kozlowski *et al.* described dendritic growth in the non-stroke hemisphere in association with behavioral recovery[58]. Immobilizing the unaffected forelimb prevented this dendritic growth and blocked behavioral recovery. Introduction of basic fibroblast growth factor (bFGF) in rats after stroke is associated with improved sensorimotor function and increased the intensity of staining for growth-associated protein 43 (GAP43) staining in the non-stroke hemisphere[59]. Staining for synaptophysin increased bilaterally when amphetamine improved behavioral outcome after stroke; improvement of behavior was linearly related to increased synaptophysin immunoreactivity[53].

The temporal course of clinical recovery after stroke parallels that of post-stroke cellular events. In untreated rats recovering from an infarct, the maximal increase in dendritic branch number occurs at day 18 (Ref. 50); in synapses per neuron, at day 30 (Ref. 52); and in synaptophysin levels, which reflects synaptogenesis, at days 14–28 post-stroke[53]. In the last study, best performances occurred at the same time-points that synaptophysin levels were at a maximum. Recovery in humans occurs over a more-protracted time-course. For example, Nakayama *et al.*[60] found that 95% of individuals achieved their final level of arm function nine weeks after a stroke. Final function was reached by six weeks in individuals with milder deficit, whereas more severely affected patients required 11 weeks. Autopsy studies could provide insights into the temporal course of growth-related proteins in humans after stroke; peak levels in the first six to eleven weeks would be expected. Such information would be important for establishing the schedule of treatments targeting post-stroke recovery.

The spatial distribution of protein changes after an infarct supports a role for these molecules in behavioral recovery. After an infarct within forelimb sensorimotor cortex, neuronal dendrite numbers increase specifically within homotopic regions of cortex in the non-lesion hemisphere[58]. Levels of GAP43, a marker of axonal outgrowth, increase exclusively in areas surrounding an acute stroke in untreated rats[59]. Increased synaptophysin staining is most intense within the same region[53]. Survival of the area surrounding an infarct has been closely linked with improved clinical outcome in humans[39], suggesting that cellular events in this area are important to the recovery process.

Clinical approaches

The analogy between development and stroke recovery could suggest clinical approaches to maximize patient outcomes. NMDA-receptor block is a strategy employed in many current therapeutic trials of acute ischemic stroke. However, during development, such inhibition is associated with reduced dendritic and synaptic pruning[61–63]. Similarly, during stroke recovery, NMDA-receptor antagonism is also associated with prevention of dendritic pruning and increased behavioral deficits[64,65]. Levels of NMDA receptors increase bilaterally after a unilateral infarct, and might be an indicator to recovery-related cortical reorganization[66].

NMDA-receptor antagonists could have deleterious clinical effects when administered beyond the acute stroke period. Conversely, we speculate that NMDA-receptor agonists administered during the quasi developmental stage after stroke might enhance functional recovery.

Specific forms of cortical-map plasticity are operative during a limited segment of development. Sensory or motor experiences during these critical periods influence adult neurological status, but after this period, the same experiences have minimal effect on subsequent neurological status[67,68]. As with developmental critical periods, there are time constraints after a stroke during which a particular experience can modify final neurological status. For example, in rats with a unilateral lesion of forelimb sensorimotor cortex, casting the intact forelimb reduces intact hemisphere dendrite expansion, decreases peri-lesional levels of bFGF, increases lesion volume and is associated with a lesser degree of recovery[58,69,70]. However, casting has these effects only when instituted during specific weeks after an infarct[71]. Similarly, osteogenic protein 1 administration improves stroke recovery without changing stroke volume when administered days, but not weeks, after an ischemic infarct in animals[72]. As a further example, promoting angiogenesis of penumbral tissue[73] and introducing exogenous stem cells within this embryonic microenvironment facilitates differentiation of the exogenous cells to parenchymal cells, and also promotes activation, proliferation and integration of endogenous subventricular zone stem cells[56,74]. Understanding the identity and temporal course of the molecules supporting developmental critical periods might be useful for maximizing clinical benefit derived from introduction of exogenous stem cells.

Some of the molecules that support developmental critical periods are also produced at increased levels after a focal infarct. For example, brain-derived neurotrophic factor (BDNF) might have a role in the activity-dependent plasticity of developing visual cortex[75]. Peri-infarct levels of this neurotrophin are known to be increased during a specific time-period after stroke[76]. Levels of VGF, a neuronal peptide precursor, peak in the brain during critical periods of development. Introduction of a cortical lesion substantially increases levels of VGF within the lesioned hemisphere[77]. Compounds such as BDNF, VGF or VGF-related proteins might be candidates for preclinical evaluation in animal models of stroke recovery.

Evidence from animal and from human studies suggests that treatments targeting stroke recovery must be linked with physical activity for benefits to be realized[78,79]. For example, a dramatic improvement in recovery is seen when rats with an experimental stroke are given amphetamine; if the drug is not paired with physical activity, however, this improvement was abolished[80]. Similarly, physical restraint can reduce post-stroke neuronal responses and impede recovery[58]. Such a bi-directional relationship between behavioral experience and brain structure during development has long been appreciated and might be of value in clarifying physiotherapy in relation to post-stroke molecular therapies.

Concluding remarks

In 1866, Haeckel proposed that ontogeny recapitulates phylogeny. Some elements of his theories have been of heuristic value. In recent decades, a number of researchers have recognized parallels that exist between stroke recovery and ontogeny, with examples described at the behavioral, brain mapping, cellular and molecular levels. Animal studies have identified treatments that improve long-term outcome by targeting the events that underlie stroke recovery[53,59,72,78]. Parallels with development might be of value in guiding treatment of stroke recovery, for example, in terms of timing of treatment, the order of molecular events to promote and the optimal micro-environment. The parallels that will be of greatest use for the treatment of individuals during stroke recovery remain to be defined.

Selected references

1 Gresham, G. *et al*. (1995) *Post-Stroke Rehabilitation*., U.S. Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research
2 Twitchell, T. (1951) Restoration of motor function following hemiplegia in man. *Brain* 74, 443–480
3 Bobath, B. (1990) *Adult Hemiplegia: Evaluation and Treatment*, Butterworth–Heinemann
4 Hines, M. (1942) The development and regression of reflexes, postures, and progression in the young Macaque. *Carnegie Institute of Washington* 54, 153–209
5 Teitelbaum, P. *et al*. (1969) Development of feeding parallels its recovery after hypothalamic damage. *J. Comp. Physiol. Psychol.* 67, 430–441
6 Wolgin, D. *et al*. (1980) Recovery of forelimb placing after lateral hypothalamic lesions in the cat: parallels and contrasts with development. *J. Comp. Physiol. Psychol.* 94, 795–807
7 Connolly, K. (1970) Skill development: problems and plans. In *Mechanisms of Motor Skill Development* (Connolly, K., ed.), pp. 3–17, Academic Press
8 Frankenburg, W.K. *et al*. (1992) The Denver II: a major revision and restandardization of the Denver Developmental Screening Test. *Pediatrics* 89, 91–97
9 Pehoski, C. (1992) Central nervous system control of precision movements of the hand. In *Development of Hand Skills in the Child* (Case-Smith, J. and Pehoski, C., eds), pp. 1–11, American Occupational Therapy Association
10 Porter, R. and Lemon, R. (1995) Developmental aspects of the corticospinal system. In *Corticospinal Function and Voluntary Movement*, pp. 96–107, Clarendon Press
11 Kim, S-G. *et al*. (1993) Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. *Science* 261, 615–617
12 Muller, K. *et al*. (1997) Ontongeny of ipsilateral corticospinal projections: a developmental study with transcrantial magnetic stimulation. *Ann. Neurol.* 42, 705–711
13 Woods, B. and Teuber, H-L. (1978) Mirror movements after childhood hemiparesis. *Neurology* 28, 1152–1158
14 Siegel, A. *et al*. (1999) Design and evaluation of a continuous-wave diffuse optical tomography system. *Optics Express* 4, 287–298
15 Weiller, C. *et al*. (1996) Brain representation of active and passive movements. *Neuroimage* 4, 105–110
16 Gaillard, W. *et al*. (2000) Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology* 54, 180–185
17 Nelles, G. *et al*. (1999) Reorganization of sensory and motor systems in hemiplegic stroke patients. A positron emission tomography study. *Stroke* 30, 1510–1516
18 Heald, A. *et al*. (1993) Longitudinal study of central motor conduction time following stroke. 1. Natural history of central motor conduction. *Brain* 116, 1355–1370
19 Turton, A. *et al*. (1996) Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. *Electroenceph. Clin. Neurophys.* 101, 316–328
20 Netz, J. *et al*. (1997) Reorganization of motor output in the non-affected hemisphere after stroke. *Brain* 120, 1579–1586
21 Weiller, C. *et al*. (1993) Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. *Ann. Neurol.* 33, 181–189
22 Cramer, S. *et al*. (1997) A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke* 28, 2518–2527
23 Cramer, S. *et al*. (1997) A functional MRI study of three motor tasks in the evaluation of recovery from stroke. *Proceedings of the Fifth Meeting of the International Society of Magnetic Resonance in Medicine (ISMRM) Vancouver*, 512
24 Cao, Y. *et al*. (1998) Pilot study of functional MRI to assess cerebral activation of motor function after poststroke hemiparesis. *Stroke* 29, 112–122
25 Cramer, S. *et al*. (1999) Distinct regions of motor cortex control ipsilateral and contralateral finger movements. *J. Neurophysiol.* 81, 383–387

26 Rao, S. *et al*. (1993) Functional magnetic resonance imaging of complex human movements. *Neurology* 43, 2311–2318
27 Garol, H. and Bucy, P. (1944) Suppression of motor response in man. *Arch. Neurol. Psychiatry* 51, 528–532
28 Luders, H. *et al*. (1995) Cortical electrical stimulation in humans. The negative motor areas. In *Negative Motor Phenomena* (Fahn, S. *et al.*, eds), pp. 115–129, Lippincott–Raven
29 Grafton, S. *et al*. (1991) Somatotopic mapping of the primary motor cortex in humans: activation studies with cerebral blood flow and positron emission tomography. *J. Neurophysiol.* 66, 735–743
30 Rao, S. *et al*. (1995) Somatotopic mapping of the human primary motor cortex with functional magnetic resonance imaging. *Neurology* 45, 919–924
31 Schieber, M. and Poliakov, A. (1998) Partial inactivation of the primary motor cortex hand area: effects on individuated finger movements. *J. Neurosci.* 18, 9038–9054
32 Sanes, J. *et al*. (1995) Shared neural substrates controlling hand movements in human motor cortex. *Science* 268, 1775–1777
33 Benecke, R. *et al*. (1991) Reorganisation of descending motor pathways in patients after hemispherectomy and severe hemispheric lesions demonstrated by magnetic brain stimulation. *Exp. Brain Res.* 83, 419–426
34 McFie, J. (1961) The effects of hemispherectomy on intellectual functioning in cases of infantile hemiplegia. *J. Neurol. Neurosurg. Psychiatry* 24, 240–249
35 Nudo, R. *et al*. (1996) Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 272, 1791–1794
36 Xerri, C. *et al*. (1998) Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys. *J. Neurophysiol.* 79, 2119–2148
37 Seitz, R. *et al*. (1998) Role of the premotor cortex in recovery from middle cerebral artery infarction. *Arch. Neurol.* 55, 1081–1088
38 Cramer, S.C. *et al*. (2000) A pilot study of somatotopic mapping after cortical infarct. *Stroke* 31, 668–671
39 Furlan, M. *et al*. (1996) Spontaneous neurological recovery after stroke and the fate of the ischemic penumbra. *Ann. Neurol.* 40, 216–226
40 Feuerstein, G. *et al*. (1997) Inflammatory gene expression in cerebral ischemia and trauma. Potential new therapeutic targets. *Ann. New York Acad. Sci.* 825, 179–193
41 Hagemann, G. *et al*. (1998) Increased long-term potentiation in the surround of experimentally induced focal cortical infarction. *Ann. Neurol.* 44, 255–258
42 Johansson, B. (2000) Brain plasticity and stroke rehabilitation: the Willis lecture. *Stroke* 31, 223–230
43 Stork, O. and Welzl, H. (1999) Memory formation and the regulation of gene expression. *Cell Mol. Life Sci.* 55, 575–592
44 Gidh-Jain, M. *et al*. (1995) Reemergence of the fetal pattern of L-type calcium channel gene expression in non infarcted myocardium during left ventricular remodeling. *Biochem. Biophys. Res. Commun.* 216, 892–897
45 Boni-Schnetzler, M. *et al*. (1989) Regulation of hepatic expression of IGF I and fetal IGF binding protein mRNA in streptozotocin-diabetic rats. *FEBS Lett.* 251, 253–256
46 Figarella-Branger, D. *et al*. (1999) Sequence of expression of MyoD1 and various cell surface and cytoskeletal proteins in regenerating mouse muscle fibers following treatment with sodium dihydrogen phosphate. *J. Neurol. Sci.* 165, 106–115
47 Reinhardt, D. *et al*. (1998) Hemoglobin F in myelodysplastic syndrome. *Ann. Hematol.* 76, 135–138
48 Huttenlocher, P. (1979) Synaptic density in human frontal cortex – developmental changes and effects of aging. *Brain Res.* 163, 195–205
49 Zecevic, N. *et al*. (1989) Changes in synaptic density in motor cortex of rhesus monkey during fetal and postnatal life. *Dev. Brain Res.* 50, 11–32
50 Jones, T. and Schallert, T. (1992) Overgrowth and pruning of dendrites in adult rats recovering from neocortical damage. *Brain Res.* 581, 156–160
51 Kolb, B. (1995) Plasticity and recovery in adulthood. In *Brain Plasticity and Behavior*, pp. 95–112, Lawrence Erlbaum and Associates
52 Jones, T. *et al*. (1996) Synaptogenesis and dendritic growth in the cortex opposite unilateral sensorimotor cortex damage in adult rats: a quantitative electron microscopic examination. *Brain Res.* 733, 142–148
53 Stroemer, R. *et al*. (1998) Enhanced neocortical neural sprouting, synaptogenesis, and behavioral recovery with D-amphetamine therapy after neocortical infarction in rats. *Stroke* 29, 2381–2395
54 Kempermann, G. *et al*. (1997) More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386, 493–495
55 Gould, E. *et al*. (1999) Neurogenesis in the neocortex of adult primates. *Science* 286, 548–552
56 Chopp, M. *et al*. (1999) Adult bone marrow transplantation for treatment of stroke in adult mice. *Soc. Neurosci. Abstr.* 25, 1309
57 Jones, T. and Schallert, T. (1994) Use-dependent growth of pyramidal neurons after neocortical damage. *J. Neurosci.* 14, 2140–2152
58 Kozlowski, D. *et al*. (1996) Use-dependent exaggeration of neuronal injury after unilateral sensorimotor cortex lesions. *J. Neurosci.* 16, 4776–4786
59 Kawamata, T. *et al*. (1997) Intracisternal basic fibroblast growth factor (bFGF) enhances functional recovery and upregulates the expression of a molecular marker of neuronal sprouting following focal cerebral infarction. *Proc. Natl. Acad. Sci. U.S.A.* 94, 8179–8184
60 Nakayama, H. *et al*. (1994) Recovery of upper extremity function in stroke patients: the Copenhagen stroke study. *Arch. Phys. Med. Rehabil.* 75, 394–398
61 Rocha, M. and Sur, M. (1995) Rapid acquisition of dendritic spines by visual thalamic neurons after blockade of *N*-methyl-D-aspartate receptors. *Proc. Natl. Acad. Sci. U. S. A.* 92, 8026–8030
62 Cramer, K. and Sur, M. (1996) The role of NMDA receptors and nitric oxide in retinogeniculate development. *Prog. Brain Res.* 108, 235–244
63 Rabacchi, S. *et al*. (1992) Involvement of the *N*-methyl D-aspartate (NMDA) receptor in synapse elimination during cerebellar development. *Science* 256, 1823–1825
64 Kozlowski, D. *et al*. (1994) Pruning of dendrites and restoration of function after brain damage: role of the NMDA receptor. *Restor. Neurol. Neurosci.* 7, 119–126
65 Barth, T. *et al*. (1998) Effects of glutamate antagonists on the recovery and maintenance of behavioral function after brain injury. In *Restorative Neurology: Advances in Pharmacotherapy for Recovery After Stroke* (Goldstein, L., ed.), pp. 121–140, Futura Publishing Company
66 Que, M. *et al*. (1999) Widespread up-regulation of *N*-methyl-D-aspartate receptors after focal photothrombotic lesion in rat brain. *Neurosci. Lett.* 273, 77–80
67 Hubel, D. and Wiesel, T. (1970) The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* 206, 419–436
68 Geschwind, N. (1974) Late changes in the nervous system: an overview. In *Plasticity and Recovery of Function in the Central Nervous System* (Stein, D. *et al.*, eds), pp. 467–508, Academic Press
69 Humm, J. *et al*. (1997) Forced disuse of the impaired forelimb by restraint after sensorimotor cortical injury inhibits expression of endogenous bFGF in astrocytes and adversely affects behavioral function. *Soc. Neurosci. Abstr.* 23, 229
70 Humm, J. *et al*. (1998) Use-dependent exacerbation of brain damage occurs during an early post-lesion vulnerable period. *Brain Res.* 783, 286–292
71 Schallert, T. *et al*. Motor rehabiliation, use–related neural events, and reorganization of the brain after injury. In *Neuroplasticity and Reorganization of Function after Brain Injury* (Grafman, J. and Levin, H., eds) (in press)
72 Ren, J. *et al*. (1999) Intravenous osteogenic protein–1 enhances functional recovery following focal cerebral ischemia in rats. *Soc. Neurosci. Abstr.* 25, 1850
73 Zhang, Z. *et al*. (1999) VEGF, flt-1, and flk–1 expression in a rat model of focal cerebral embolic ischemia. *Stroke* 30, 232
74 Chen, J. *et al*. Intracerebral transplantation of bone marrow with BDNF after MCAo in rat. *Neuropharmacology* (in press)
75 Rossi, F. *et al*. (1999) Monocular deprivation decreases brain-derived neurotrophic factor immunoreactivity in the rat visual cortex. *Neuroscience* 90, 363–368
76 Comelli, M. *et al*. (1993) Time course, localization and pharmacological modulation of immediate early inducible genes, brain-derived neurotrophic factor and trkB messenger RNAs in the rat brain following photochemical stroke. *Neuroscience* 55, 473–490
77 Snyder, S. *et al*. (1998) The messenger RNA encoding VGF, a neuronal peptide precursor, is rapidly regulated in the rat central nervous system by neuronal activity, seizure and lesion. *Neuroscience* 82, 7–19
78 Cramer, S. and Finklestein, S. (1999) Reparative approaches: growth factors and other pharmacological treatments. In *Stroke Therapy: Basic, Preclinical, and Clinical Directions* (Miller, L., ed.), pp. 321–336, John Wiley
79 Dobkin, B. (1996) Plasticity in motor and cognitive networks. In *Neurologic Rehabilitation*, pp. 3–45, FA Davis
80 Feeney, D. *et al*. (1982) Amphetamine, halperidol, and experience interact to affect the rate of recovery after motor cortex injury. *Science* 217, 855–857
81 Chopp, M. and Li, Y. (1998) Protein expression: cerebral damage and opportunity for tissue repair after experimental stroke. Proceedings of the 7th International Symposium on Pharmacology of Cerebral Ischemia. In *Pharmacology of Cerebral Ischemia 1998* (Krieglstein, J., ed.), pp. 401–405, Medpharm Scientific Publishers
82 Duggal, N. *et al*. (1997) Nestin expression in reactive astrocytes following focal cerebral ischemia in rats. *Brain Res.* 768, 1–9
83 Li, Y. and Chopp, M. (1999) Temporal profile of nestin expression after focal cerebral ischemia in adult rat. *Brain Res.* 838, 1–10
84 Li, Y. *et al*. (1998) Neuronal damage and plasticity identified by MAP-2, GAP-43 and cyclin D1 immunoreactivity after focal cerebral ischemia in rat. *Stroke* 29, 1972–1981
85 Stroemer, R. *et al*. (1995) Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. *Stroke* 26, 2135–2144

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86 Lin, T. *et al*. (1997) Induction of basic fibroblast growth factor (bFGF) expression following focal cerebral ischemia. *Mol. Brain Res*. 49, 255–265
87 Hayashi, T. *et al*. (1997) Rapid induction of vascular endothelial growth factor gene expression after transient middle cerebral artery occlusion in rats. *Stroke* 28, 2039–2044
88 Chopp, M. *et al*. (1992) p53 expression in brain after middle cerebral artery occlusion in the rat. *Biochem. Biophys. Res. Commun*. 182, 1201–1207
89 Li, Y. *et al*. (1997) Apoptosis and protein expression after focal cerebral ischemia in rat. *Brain Res*. 765, 301–312
90 Chen, J. *et al*. (1996) Expression of the apoptosis-effector gene, Bax, is up-regulated in vulnerable hippocampal CA1 neurons following global ischemia. *J. Neurochem*. 67, 64–71
91 Timsit, S. *et al*. (1999) Increased cyclin D1 in vulnerable neurons in the hippocampus after ischaemia and epilepsy: a modulator of *in vivo* programmed cell death? *Eur. J. Neurosci*. 11, 263–278

Arbitrary associations between antecedents and actions

Steven P. Wise and Elisabeth A. Murray

The arbitrary linkage of sensory cues to actions and goals represents one of the most-flexible capabilities in the behavioral repertoire of mammals. This ability has been termed 'conditional motor learning', 'conditional discrimination' or, more recently, 'arbitrary visuomotor mapping'. Unlike other forms of visuomotor guidance, in arbitrary mapping the location of the sensory cue lacks any systematic spatial relationship with the action or its goal. Recent work has identified much of the neural network that underlies this behavior. It consists of parts of the frontal cortex, hippocampal system and basal ganglia, each of which has neurons whose activity undergoes systematic evolution during learning.

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> Some of the psychological papers at the meeting were impressive…, but there were other kinds of papers, too – P.T. Zellerman's study on the difference in the length of time it took white rats to learn a maze when the corners were curved rather than angular, or Worfel's paper on the effect of intelligence level on the reaction time of rhesus monkeys. Papers like these made me angry. Money, time, and energy squandered on the detailed analysis of the trivial.
>
> Daniel Keyes[1]

THIS QUOTATION comes from Charlie Gordon, who, together with a mouse named Algernon, had genius thrust upon him by an experimental brain lesion. We need not share Charlie's scepticism about spatial-memory and reaction-time studies; he is, after all, fictional. If, as Charlie implies, simply remembering places and reacting faster are relatively unimposing cognitive functions, what kind of behavior might be more impressive, yet amenable to laboratory study?

One potential answer involves conditional motor learning, the arbitrary association between stimuli and actions[2]. This capability supercedes the simple storage of sensory information, such as remembering a place, and it epitomizes the behavioral flexibility that makes up an important aspect of intelligent behavior. Unfortunately, the phrase 'conditional motor learning' often generates misunderstanding. The 'conditional' term causes confusion with conditioned reflexes, which, unlike conditional motor learning, depend on unconditioned reflexes. The 'motor learning' part evokes images of skill acquisition, with which conditional motor learning has even less in common. An alternative terminology relies on propositional logic, 'if antecedent, then consequent'. Using this vocabulary, we can say that an antecedent maps arbitrarily onto a consequent. When visual cues serve as antecedents and movements as consequents, the result can be called arbitrary visuomotor mapping.

Movements usually have spatial targets, and so visuomotor and visuospatial mapping will be discussed together, emphasizing their common feature: arbitrary use of nonspatial visual cues to produce a clearly observable action. These features have considerable practical value in the laboratory. However, arbitrary visuomotor mapping is no mere laboratory curiosity; it has fundamental importance in human behavior. Without this ability, drivers could not learn to stop at red traffic signals (or, failing that, at least slow down). More generally, signal-guided or symbolically guided actions would be impossible. Arbitrary visuomotor mapping is, we would submit to Charlie Gordon, a higher brain function worthy of 'money, time, and energy'.

Ablations

One central issue concerns which neural structures compute these flexible mappings. Neuropsychological research has identified the basic components of a widely distributed neural network underlying this function. The study of arbitrary visuomotor mapping dates back at least to the early 1970s, but the most influential work was carried out more recently, predominantly in the laboratories of Richard Passingham, Michael Petrides and David Gaffan[3]. The work of Passingham and Petrides showed that ablations of the dorsal premotor cortex, a part of the frontal lobe situated between the prefrontal and primary motor areas (PMd in Fig. 1), caused serious deficits in learning arbitrary visuomotor mappings. For example, monkeys with PMd lesions could not learn to twist a handle in response to a yellow placard, although they performed normally in both twisting the handle

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