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NEW TREATMENTS IN NEUROREHABILITATION FOUNDED ON BASIC RESEARCH

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Recent discoveries about how the central nervous system responds to injury and how patients reacquire lost behaviours by training have yielded promising new therapies for neurorehabilitation. Until recently, this field had been largely static, but the current melding of basic behavioural science with neuroscience promises entirely new approaches to improving behavioural, perceptual and cognitive capabilities after neurological damage. Studies of phenomena such as cortical reorganization after a lesion, central nervous system repair, and the substantial enhancement of extremity use and linguistic function by behavioural therapy, support this emerging view. The ongoing changes in rehabilitation strategies might well amount to an impending paradigm shift in this field.

The relative dearth of effective interventions in neurorehabilitation could be partly attributable to the weak contribution that this field has received from basic sciences such as neuroscience and behavioural psychology. Neuroscience holds an important place in the curriculum of physical therapy schools, but its influence has been largely didactic and has had little bearing on clinical practice. Behavioural psychology has contributed much to the treatment of chronic pain[1], but has little or no place in the curriculum of physical rehabilitation schools or in the development of treatments for movement disorders. In other health-related fields, basic research has, of course, been of inestimable value in enabling the development of new therapeutic interventions. In the neurosciences, the fruitfulness of this approach has been amply shown by the development of treatments for Parkinson's disease and other disorders on the basis of the pioneering work of Carlsson and others on chemical neurotransmission[2,3]. The paradigm shift that is mentioned in the preface refers to the fact that this process of translation of basic research into new treatments is beginning to take place in the field of neurorehabilitation and is proceeding at an accelerating pace.

After injury to the central nervous system (CNS), the initial deficit in behaviour, perception and/or cognitive ability is frequently followed by a spontaneous recovery of function. This resiliency may be considered as one type of behavioural plasticity. By apparent contrast, the traditional view in neuroscience during the first three-quarters of the last century was that the mature CNS has little capacity to reorganize and repair itself in response to injury. This view extends back into the nineteenth century, promoted initially by Broca's studies on the localization of function within the brain[4], which emphasized the constancy of organization of the mature CNS even after substantial injury. Although contrary views were expressed[5,6], the mature CNS was generally believed[7] to show little or no plasticity[8]. Hughlings Jackson's hierarchical view[9] that lower centres of the brain substituted in function for higher damaged centres after CNS insult, together with other related formulations, had an important influence for most of the twentieth century on our thinking about the recovery of function. However, the phenomenon of spontaneous recovery of function was never fully explained and received little experimental attention, largely because the techniques needed to explore this process had not yet been developed. Beginning in the 1970s, research from several laboratories, including those of Merzenich[10], Kaas[11] and Wall[12], showed that, contrary to the established belief, the adult

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CONDITIONED RESPONSE TECHNIQUES
Methods inspired by studies of operant conditioning in which a specified response is strengthened or increased in frequency by presenting a reward after its performance.

SHAPING
An operant training method in which a desired motor or behavioural objective is approached in small steps — by successive approximations — so that the improvement required for successful performance at any point in the training programme is small.

mammalian CNS does have some capacity to reorganize itself functionally after injury. At the level of the cerebral cortex, this phenomenon is usually referred to as cortical reorganization[13,14]. The question naturally arises as to whether there is some relationship between the spontaneous recovery that occurs after CNS damage, and cortical plasticity. Ultimately, we would like to know whether this relationship could be manipulated to improve the potential for recovering function, so that it would be advantageous to a patient with neurological injury. A line of research that begins with somatosensory deafferentation in monkeys and progresses to a new treatment for humans after stroke and other types of neurological damage can be viewed as a model for addressing this question.

From deafferentation to CI therapy

Basic research with monkeys. When somatic sensation is surgically abolished from a single forelimb in a monkey, the animal does not make use of it in the free situation[15]. This is the case even though the motor outflow through the ventral roots remains intact. However, monkeys can be induced to use the deafferented extremity by restricting movement of the intact limb continuously for a period of days[16,17]. The monkey may not have used the affected extremity for several years, but the application of this simple technique results in a conversion of the useless forelimb into a limb that is used for a wide variety of purposes for the rest of the animal's life[18,19]. The movements are not normal: they are clumsy because somatic sensation has been abolished, but they are extensive and effective. This can be considered as a substantial rehabilitation of movement.

Training procedures are another means of overcoming the lack of use of a single deafferented limb in primates[18]. Transfer from the experimental to the real-life situation was never observed when using CONDITIONED RESPONSE TECHNIQUES to train limb use. But when the training technique termed SHAPING[20,21] was used, there was substantial improvement in the motor ability of the deafferented limb in the real-life situation[18]. Shaping

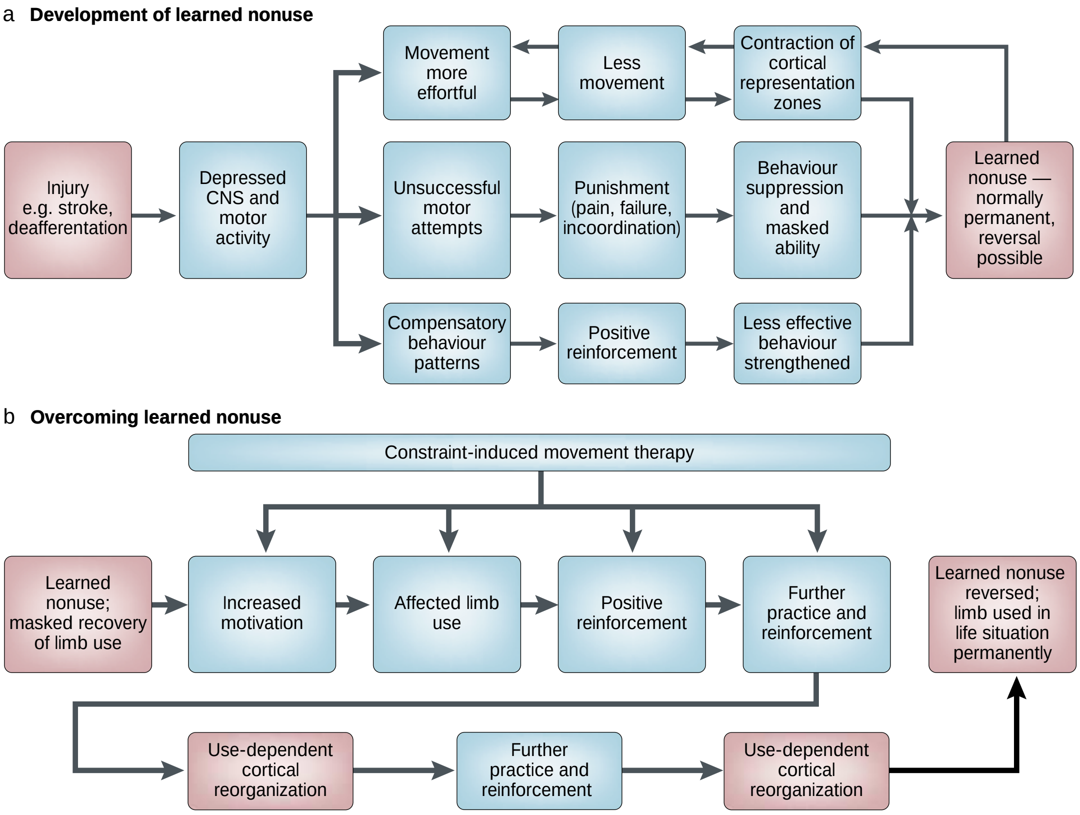

Figure 1 | **Development and overcoming of 'learned nonuse' of an upper extremity. a** | Substantial neurological injury usually leads to a substantial depression in motor and/or perceptual function. During this period, the subject cannot use the affected extremity effectively. Attempts to use the affected limb generally lead to failure. These punishing consequences result in suppression of the use of the limb (middle row). Moreover, the subject might manage reasonably well using only the uninvolved upper extremity, and is therefore rewarded for this pattern of behaviour, which as a result is strengthened (bottom row). In addition, after stroke[36,37], and presumably after extremity deafferentation, there is a marked contraction in the size of the cortical representation of the limb. This probably correlates with the report of patients with stroke that movement of that extremity is effortful (top row). These three processes interact to produce a vicious downward spiral that results in 'learned nonuse' of the affected extremity, which is normally permanent. **b** | When appropriate techniques are applied, learned nonuse can be overcome. Training procedures can be used to reward patients systematically for using the affected arm for a period of consecutive weeks. In addition, use of the uninvolved limb can be restricted, such that the subject is rendered virtually helpless unless he/she tries to use the affected limb. Increased use of the limb leads to a use-dependent enlargement of the cortical representation of the affected extremity[36,37], which reduces the effort in using it and provides a neural basis for the long-term retention of gains made in the laboratory or clinic. (CNS, central nervous system.)

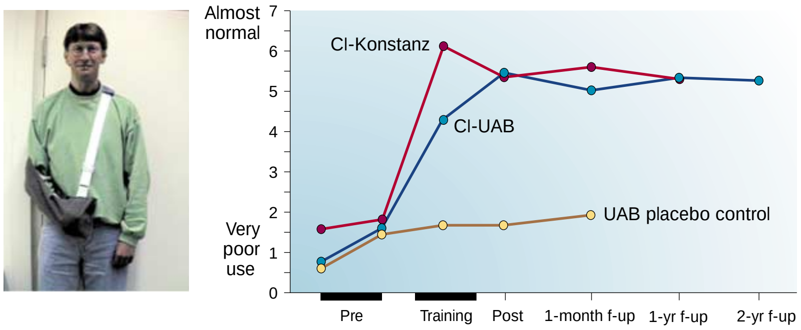

Figure 2 | **Constraint-Induced Movement therapy.** Constraint-Induced (CI) Movement therapy involves constraining the movement of the extremity that is less affected by cerebral nervous system injury and, more importantly, 'shaping' the affected limb (an arm in this case) for many hours a day for two or three consecutive weeks. The constraint, by a sling or a mitt, forces the individual to make use of the more affected extremity. The quality or skill of the movements is systematically improved by a shaping procedure. This method was derived from work with monkeys that would not make use of a deafferented arm, but readily learned to use this extremity either through shaping or when the constraining device prevented movements of the intact arm. The data show a large increase in real-life arm use in a CI therapy group trained at the University of Alabama at Birmingham (UAB), and the close replication of this result in a group treated at the University of Konstanz. A placebo group that received a general fitness programme did not show a significant change over time. (f-up, follow-up study.)

produced an almost complete reversal of the motor disability, which progressed from total absence of the target behaviour to very good (although not normal) performance that transferred from the training to the free, colony environment.

During the course of the past century, several other investigators have found that a behavioural technique can be used in animals to improve motor performance substantially after neurological damage[22–25]. However, none of these observations was embedded in a formal theoretical context that allowed the formulation of predictions, nor was the generality of the mechanisms clearly recognized. Consequently, these findings remained a set of disconnected observations.

A possible mechanism: learned nonuse. Several converging lines of evidence indicate that nonuse of a single deafferented limb is a learning phenomenon that involves a behaviourally reinforced suppression of movement known as 'learned nonuse'. The restraint and training techniques seem to be effective because they overcome learned nonuse. The process by which this phenomenon develops and can be overcome by an appropriate behavioural method is shown in FIG. 1.

Applicability to humans after stroke. Given the general applicability of the learned-nonuse formulation to motor status after many types of neurological damage, it was reasoned that the Constraint-Induced (CI) Movement techniques that had been developed in experiments with monkeys might represent an appropriate approach to the rehabilitation of motor disability in humans after CNS injury. For example, stroke often leaves patients with an apparently permanent loss of function in an upper extremity, even though the limb is not paralysed. Furthermore, the motor impairment is preponderantly unilateral. These features are similar to those seen after unilateral forelimb deafferentation in monkeys. Therefore, it seemed reasonable to formulate a protocol that simply transferred the techniques used in monkeys for overcoming learned nonuse of a deafferented limb to humans who had experienced a cerebrovascular accident[19].

The protocol[19] recommended both training of the paretic arm and restraint of the contralateral arm. The initial applications of CI movement therapy to humans after stroke[27–30] did not make use of the full protocol and, although the results were promising, the treatment effects were small. Taub and co-workers[31] applied both parts of the CI therapy protocol to the rehabilitation of patients with a chronic upper extremity hemiparesis in a study that emphasized the transfer of therapeutic gains in the laboratory to the real-life situation. Patients with chronic symptoms of stroke (more than four years on average) were selected to participate, as the literature and general clinical experience supported the view that motor recovery usually reaches a plateau within one year after stroke and is not amenable to further modification.

The participants wore a sling on their less affected arm during 90% of their waking hours for 14 days. On ten of those days, they received six hours of training of their more affected arm. Control participants were told that they had much greater movement of their more affected limb than they were actually showing, were led through a series of passive movement exercises in the treatment centre, and were given passive movement exercises to perform at home. The treated group showed a significant increase in the skill or quality of movement, as measured by two laboratory motor tests, and a much larger increase in real-world arm use over the two-week period. Moreover, they showed no decrease in real-world arm use when tested two years after the treatment. The control subjects showed no change or a decline in real-life arm use over the same period.

These results (FIG. 2) have been confirmed in another placebo-controlled experiment[26], and further work has indicated that there is a family of techniques that can be used to overcome learned nonuse[32–35]. Although most of the techniques involve constraining movement of the less affected arm, two of them do not. The common factor seems to be repeatedly training the paretic arm. Any technique that induces a patient to use an affected extremity for many hours a day for a period of consecutive weeks should be therapeutically efficacious. This factor is likely to produce the use-dependent cortical reorganization that was recently found to result from CI therapy[36–39] (see below), and is presumed to be the basis of the long-term increase in the amount of use of the more affected extremity. Mauritz and co-workers[40,41] have also shown that repetitive practice is an important factor in stroke rehabilitation.

The beneficial effect of CI therapy on the functioning of the upper extremities has been replicated in several laboratories for the chronic symptoms of stroke[42–45] and for acute symptoms in the period beginning 7–14 days after stroke[46]. A six-site randomized US clinical trial of CI therapy in the subacute period is now underway. At the University of Alabama at Birmingham,

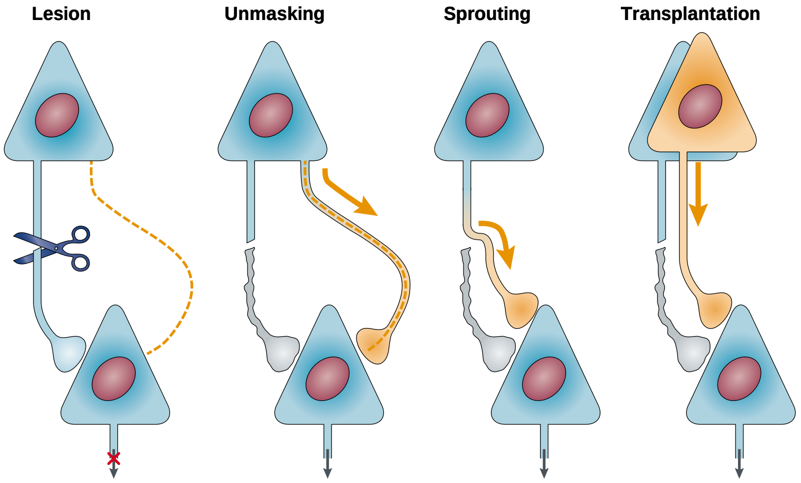

Figure 3 | **Types of recovery.** A central nervous system (CNS) lesion results in two forms of damage: neuronal cell death and deafferentation resulting from interruption of activity in neural networks. The latter process causes a much greater initial loss of function than could be accounted for by the loss of neurons. Several processes can restore the functioning of the network and lead to recovery: remaining connections within damaged cell assemblies can be strengthened, silent pathways can be unmasked, and axonal sprouting can bridge disruptions that result from the damage. In the future, it might also be possible to reduce the consequences of CNS damage through transplantation.

nearly 300 patients have been treated so far, and the treatment has been incorporated into a routine clinical setting. The EFFECT SIZE for transfer of treatment outcome to daily activities in the real world varies from 2.1 to 4.0, depending on the experiment (0.8 is considered by convention to be a large effect size[47]). More recent work with patients with a more severe motor deficit indicates that motor ability is modifiable in the upper 65–75% of the population with chronic symptoms of stroke, in terms of severity of their motor deficit.

Reorganization in response to treatment. Evidence from several studies indicates that the size of the cortical representation of a body part in adult humans depends on the amount of use of that part[48–50]. Moreover, focal TRANSCRANIAL MAGNETIC STIMULATION (TMS), MAGNETIC SOURCE IMAGING and READINESS POTENTIAL studies in humans, and intracortical microstimulation in monkeys, indicate that cortical reorganization might be associated with the positive effect of CI therapy. Potential neural mechanisms that could underlie the observed recovery are illustrated in FIG. 3.

Nudo and co-workers[51] carried out a groundbreaking intracortical microstimulation study in adult squirrel monkeys in which an ischaemic infarct was produced surgically in the cortical area that controls the movements of a paw. The study showed that training of the more affected limb resulted in cortical reorganization. Specifically, the area surrounding the infarct, which would not normally be involved in control of the paw, began to participate in those movements (FIG. 4).

Liepert and co-workers[36] provided the first demonstration that CI therapy produces a large, use-dependent cortical reorganization in humans with stroke-related paresis of an upper extremity. They used focal TMS to map the area of the primary motor cortex that controls arm movement in six patients with chronic upper limb hemiparesis, before and after CI therapy. The clinical findings replicated the previously reported improvement in real-life arm use. In addition, the cortical region from which TMS could elicit electromyographic responses of a hand muscle was greatly increased. In a follow-up study with nine further patients, motor rehabilitation and the alteration in brain function persisted for the six months of follow-up[37]. CI therapy had led to the recruitment of a large number of neurons to participate in movements of the more affected upper extremity. These neurons were adjacent to those originally involved in control of the limb. The area of excitability for the muscle had become equal on the two sides of the brain. Kopp and co-workers[38] carried out a current-source density analysis of the steady-state electroencephalographic motor potential of CI therapy patients. Three months after treatment, the motor cortex ipsilateral to the more affected arm had been recruited to generate movements of that extremity. This effect was not evident immediately after treatment, and was presumably due to a sustained increase in the use of the more affected arm after CI therapy over the three-month follow-up period. Moreover, Bauder and colleagues[39] have shown that CI therapy greatly increases the amplitude of the late components of the readiness potential.

These findings indicate that CI therapy might produce a permanent increase in arm use by two related, but distinctly different, mechanisms. First, CI therapy changes the contingencies of reinforcement so that nonuse of the more affected extremity, which is learned in the acute and early subacute periods, is counterconditioned or lifted. In other words, by training the more affected arm and constraining the less affected arm, CI therapy provides opportunities for positively reinforcing the use of the more affected extremity and adverse consequences for its nonuse. Second, the consequent increase in use, which involves sustained and repeated practice of functional arm movements, induces expansion of the contralateral cortical area that controls movement of the more affected extremity and recruitment of new ipsilateral areas. This use-dependent cortical reorganization could serve as the neural basis of the permanent increase in use of the more affected arm. Moreover, these studies show an alteration in brain organization or function that is associated with a therapy-induced improvement in the rehabilitation of movement after CNS damage.

Boundaries of CI therapy. CI therapy does not make movement normal. When patients with chronic symptoms of stroke have received training of adequate intensity, this treatment has produced substantial improvements in virtually all of the ~300 people studied so far[26]. However, the improvement does not restore to patients the motor status that they had before the cerebral vascular accident. Although impairment and disability have been meaningfully reduced by the completion of treatment, there is typically still a deficit.

CI therapy produces a variable outcome that depends on the severity of the initial impairment. If stroke

EFFECT SIZE
A measure of effect that is adopted when different scales are used to measure an outcome. It is usually defined as the difference in means between the experimental and control groups, divided by the standard deviation of the control or both groups. As effect size is a standardized measure, it allows us to compare and/or combine the effects found in different studies of the same phenomenon.

TRANSCRANIAL MAGNETIC STIMULATION
A technique used to induce a transient stimulation of activity in a relatively restricted area of the brain. It is based on the generation of a strong magnetic field near the area of interest, which, if changed rapidly enough, will induce an electric field that is sufficient to stimulate neurons.

MAGNETIC SOURCE IMAGING
The detection of the changing magnetic fields that are associated with brain activity, and their subsequent overlaying on magnetic resonance images to identify the precise source of the signal.

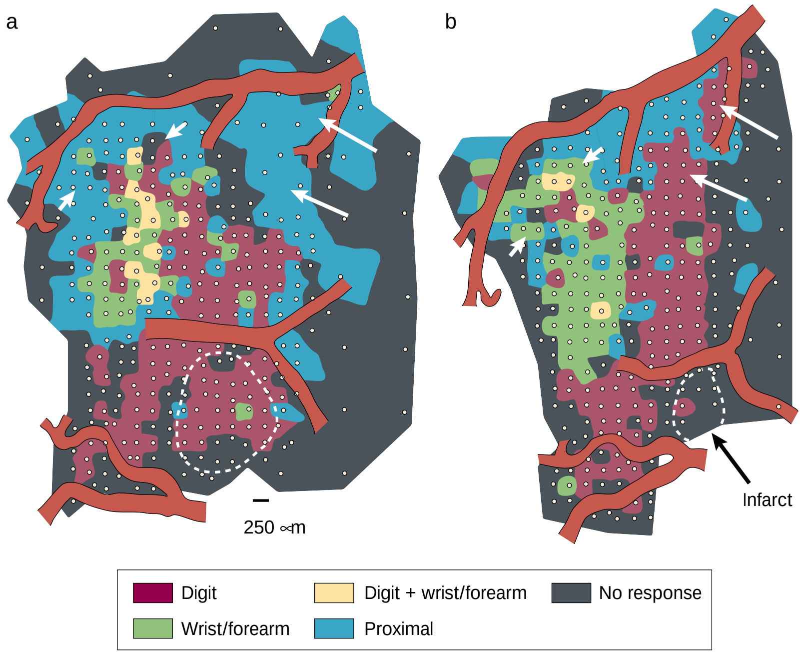

Figure 4 | **Reorganization in the motor cortex of a monkey after rehabilitative therapy.** **a** | Before infarct. **b** | After infarct and rehabilitative therapy. Note the large increase in the cortical representation of the wrist/forearm after therapy. Adapted with permission from REF. 51 © 1996 American Association for the Advancement of Science.

patients with residual motor deficits are divided on the basis of their active range of motion, the upper 25% of the population tend to improve more than patients from the next 50% (REF. 26). Although the short-term relative change is similar, albeit somewhat reduced in second- and third-quartile patients, the absolute level of motor function is lower, as these people start treatment from a lower level in terms of amount of use.

For patients from the lowest quartile of motor functioning, CI therapy does improve movement at the shoulder and elbow. However, as they have little or no ability to move the fingers, there is no adequate motor basis for carrying out training of hand function. Consequently, as most daily activities that are carried out by the upper extremity are performed by the hand, there is relatively little translation of the therapy-induced improvement in proximal joint function into an increase in the actual amount of use of the more affected extremity in the real-life situation.

Patients with higher function have been found to retain their treatment gains without decrement for the two years that they have been tested. However, patients from the second and third quartiles do show a decrement of ~20% one year after treatment and greater loss after two years. This indicates that it might be important to consider short 'brush-up' periods of training to maintain the treatment gains in these patients.

So, CI therapy is clearly not a complete answer to motor deficit after stroke. However, the work so far does show that motor function in about three-quarters of patients with chronic stroke is substantially modifiable. This modifiability of motor ability, which presumably reflects the CNS plasticity that has been shown to occur as a result of CI therapy, can therefore be used to improve the therapeutic outcome of patients with stroke and other types of neurological injury.

Other applications of CI therapy

The range of disorders for which CI therapy might be an effective treatment encompasses several conditions in which motor disability is in apparent excess to the underlying brain pathology. Our research indicates that excess disability is an important component of many conditions that include motor impairment and are refractory to current forms of treatment. As discussed above, the signature CI therapy intervention is used for stroke patients with an upper extremity paresis. The original therapy has recently been extended in our laboratory to treat deficits in arm use in people with traumatic brain injury[52], cerebral palsy (E.T., S. C. DeLuca, K. Echols and S. L. Ramey, unpublished observations), FOCAL HAND DYSTONIA[53,54], phantom limb pain[55] and APHASIA[56], and to treat lower limb impairments in people with chronic stroke, spinal cord injury and hip fractures[26].

Aphasia. The demonstration that motor behaviour is modifiable in patients with chronic stroke indicates that language impairment, another consequence of stroke that often has an important motor component, might be sufficiently plastic to be rehabilitated by an appropriate modification of the CI therapy techniques. In a study by Pulvermüller and co-workers[56], people with stroke-induced aphasia received CI Aphasia therapy. These patients had previously received extensive conventional speech therapy and had reached an apparent maximum recovery of language function. They were constrained to communicate by talking, improving their language skills for three hours on each weekday over a two-week period. Groups of three patients and a therapist participated in a language game in which success was achieved by progressively improving the naming of pictured objects and explicitly requesting that other participants conform to the rules of the game[57]. In comparison with patients that received the routine treatment of the institution, the first nine CI-treated patients improved substantially, both in performance on experimental tests of language ability and in the amount of talking they did in real life[56]. Several procedures that were used in this work were developed on the basis of the CI therapy model of motor rehabilitation. They included extended, intensive practice, constraining patients to communicate using speech during the language game, shaping speech during the game, and placing emphasis on assessing the patients' real-life behaviour.

Focal hand dystonia. An intervention related to CI therapy was developed for the treatment of focal hand dystonia, a condition that involves manual incoordination in people, including musicians, who engage in extensive and forceful use of the digits. Using magnetic source imaging, it was found that musicians with focal hand dystonia show a use-dependent overlap or smearing of the representational zones of the digits of the dystonic

READINESS POTENTIAL
A broad negativity in the electroencephalogram that begins 300–3,000 ms before voluntary movements. One peculiarity of the readiness potential is that, whereas most event-related potential are time-locked to the arrival of an input, the readiness potential is time-locked to an output and always precedes it.

FOCAL HAND DYSTONIA
Manual incoordination in people that engage in extensive and forceful use of the digits.

APHASIA
A language impairment that is acquired as a result of stroke or other brain injury.

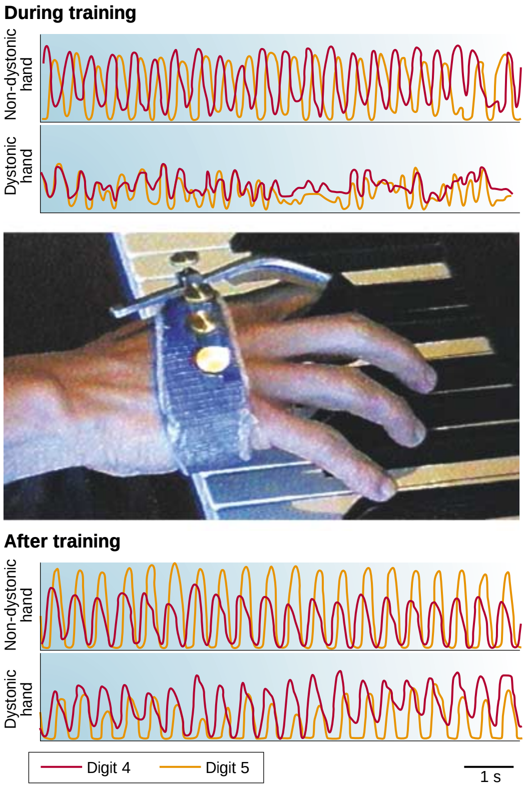

Figure 5 | **Change in motor coordination and movement pattern in musicians as a result of therapy.** The middle panel shows the cuff and splint arrangement that was used to immobilize the finger(s) during treatment. The curves show motor coordination recorded by a dexterity-displacement device before (upper panel) and after (lower panel) treatment. The device continuously recorded digital displacement during metronome-paced movements of two fingers that were carried out for 50 s with all fingers free. After training (lower panel), the pattern becomes more regular (bottom trace in lower panel) than that seen before treatment (bottom trace in upper panel). Spectral analysis of the records (not shown) provided information concerning the smoothness of the movements before, during and after training[54].

hand in the somatosensory cortex[58,59]. Digit overuse had previously been found to produce a similar phenomenon in monkeys[60]. As behavioural mechanisms seem to underlie both the cortical disorder and the involuntary incoordination of movement, it was proposed that a behavioural intervention might be of value in reducing or eliminating these conditions.

Professional musicians with long-standing symptoms were studied; they had previously received several different treatments without success[53,54]. The therapy involved the use of splints to immobilize one or more digits other than the dystonic finger (FIG. 5). The musicians were required to carry out repetitive exercises with the dystonic finger in coordination with one or more of the other digits for 1.5–2.5 hours daily over a period of eight consecutive days. All the patients showed significant improvements when operating without the splint at the end of treatment. Half of them returned to the normal or almost normal range of digit function in music performance, and the improvement of all but one patient (who did not carry out the required home practice) persisted for the 24 months of follow-up. As in the case of the aphasia treatment, treatment of focal hand dystonia has several elements in common with CI therapy for the extremities: massing the amount of practice, shaping finger placement and other aspects of motor performance, and performing the exercises while a body part is restrained.

From cortical reorganization to dyslexia

The efficacy of CI therapy in different disorders is based largely on its derivation from a body of replicated and generally accepted basic research. However, CI therapy is not alone in this regard. Research using CI therapy might be part of the leading edge of an impending paradigm shift in which other advances in behavioural science and neuroscience are used for the development of new strategies in the field of rehabilitation. An important case in point is the intervention developed by Merzenich, Tallal and co-workers[61,62] for use in children with specific language impairments (SLI) and dyslexia. Children with SLI show limitations in a wide range of expressive and/or receptive oral abilities; for example, poor vocabulary, and deficits in syntax production or comprehension. Children with SLI generally develop difficulties in reading, writing and spelling (that is, they become dyslexic), despite having normal intellectual capacity. The remedial treatment of SLI includes an important component that is derived from basic research on language functions in SLI and dyslexic children. Psychoacoustic studies have shown that auditory phoneme processing is deficient in many children with SLI and dyslexia[63,64]. Compared with children who develop language normally, those with SLI have greater difficulty in integrating brief and rapidly changing sounds. They therefore experience difficulties in discriminating stop-consonant–vowel syllables, which have short transitional periods. That this might constitute a basic impairment is supported by the fact that deficits in stop-consonant perception are, in fact, highly correlated with the language comprehension scores of SLI children. The impairment can be overcome by synthetically extending the brief transitional periods.

Recent studies using magnetoencephalography (MEG) point to abnormalities in the hemispheric asymmetry of the temporal lobe. For instance, stimulation by stop-consonant–vowel syllables generated sources of activity after 200 ms (but not earlier) that differed in their location in the auditory cortex between children with dyslexia and control children[65]. The finding cannot be attributed to gross anatomical variations. It seems to signify an abnormal functional organization of auditory cortex in children with dyslexia, and confirms the suggestion that impaired perception of rapidly changing auditory information might impede the development of language-specific phoneme representations during early infancy. Malformed cortical representation of phonemes might, in turn, lead to language-acquisition problems and subsequent difficulties in mastering the phoneme–grapheme correspondences that underlie reading and spelling. Using the principles of cortical reorganization, Merzenich *et al.*[61] and Tallal *et al.*[62] designed a computer-based training programme and showed that impaired processing of

SPECIFIC LANGUAGE IMPAIRMENT
A term that is often assigned to developmental language disorders that do not have any other apparent social, psychological or neurological cause.

DYSLEXIA
Difficulty in learning to write, spell and read that is observed in people of otherwise normal intelligence. In some cases, a genetic cause is suspected.

STOP CONSONANT
Spoken sounds vary depending on the degree of air-stream opening. Vowels are the most open sounds, followed by liquid, nasal, fricative and stop consonants, in which the air stream is maximally obstructed. In English, the six stop consonants are p, t, k, b, d and g.

MAGNETOENCEPHALOGRAPHY
A non-invasive technique that allows the detection of the changing magnetic fields that are associated with brain activity. As the magnetic fields of the brain are very weak, extremely sensitive magnetic detectors known as superconducting quantum interference devices, which work at very low, superconducting temperatures (–269 °C), are used to pick up the signal.

rapidly changing sounds could be remarkably improved in 5–10-year-old children with SLI. Children were trained with audiovisual 'games' for ~100 minutes a day, five days a week, for 20 training days. Rapid transitional speech and non-speech stimuli were initially disambiguated by extending them in time and/or amplifying them. As training progressed and the children showed success, the modified acoustic stimuli were presented in progressively less modified form until the stimuli approximated sounds as they occur in natural speech. So, as in the case of CI therapy, the training protocol involved a shaping procedure. Moreover, the therapy had to be "applied with a heavy schedule" on successive days, and required "intense practice schedules" (massed practice, again as in CI therapy) and "high motivational drive"[61]. These characteristics originated in studies of plasticity, many of which were carried out in Merzenich's own laboratory[48]. Seven per cent of preschool children are estimated to suffer from SLI, and prevalence estimates for dyslexia vary between 4 and 9% (REF. 66). Therefore, this treatment might be beneficial to large numbers of children.

Both CI therapy and the intervention against dyslexia depend, in part, on manipulations that produce a use-dependent alteration in task-related portions of the brain through the massed repetition of appropriate experiences. Heim *et al.*[65] recently showed, in a small group of children with symptoms of dyslexia, that differences in hemispheric functional organization can indeed be altered by linguistic training. We are only now beginning to tap into the potential for extending this approach to other conditions for which effective treatments do not exist at present.

Box 1 | Sensory prostheses

Sensory prostheses involve the use of real-time, direct interfaces between the brain and electronic or mechanical devices. In the context of rehabilitation, they can be used to provide a person with information that is not available from a seriously defective or inoperative sensory system. Cochlear implants were the first type of sensory prosthesis to be developed. The breakthrough in this area was achieved by the introduction of digital intracochlear multichannel systems[86]; these were developed as a result of a detailed understanding of cochlear function through research that allowed electrically elicited hearing sensations to become increasingly natural. In 1957, Djourno stimulated the auditory nerve of rabbits and verified its efficacy through electroencephalographic measurements. The first patient was operated on shortly after these studies, electrodes being placed on the auditory nerve[87]. This study was followed by the work of House[88] and, importantly, of Simmons[89], who reported the implantation of a hard-wired cluster of six stainless steel electrodes into the cochlea[89]. An increasing understanding of cochlear function and the generation of receptor potentials that activate the auditory nerve made it possible to improve the quality of the implants to such an extent that close-to-normal auditory functioning can now be achieved or regained in many people.

Another particularly fruitful approach to sensory prosthesis is a tactile vision-substitution system that was pioneered by Bach-y-Rita. This work was begun in the 1960s (REF. 90), when input from a small television camera attached to a helmet was transduced onto a tactile stimulation grid that was placed on the shoulder or abdomen. Tactile spatial discrimination is not precise in these regions and the visual resolution achieved in this early work was rudimentary. However, a very sensitive human–machine interface that operates through the tongue has recently been developed[91,92]. Before training with the prosthesis, the visual acuity of the participants averaged 20/800, but it doubled after nine hours of training. This type of interface could lead to devices that allow perceptual ability of practical significance in individuals who are blind or have other types of sensory loss. Moreover, such a device also opens up the possibility of sensory augmentation in normally endowed individuals, such as infrared detection for night vision or perception of activity in other ranges of the electromagnetic spectrum, as well as for improving the function of sensate robots, and sensate telecommunications. Combining progress in microtechnology with our rapidly increasing knowledge of the neural code, it is possible to imagine a future in which implanted chips could serve as an interface to the world.

Other therapies emerging from basic research

There are other new approaches to rehabilitation that are beginning to emerge from the melding of basic research in behavioural science and neuroscience. For example, several laboratories have developed a new strategy for the rehabilitation of lower limb function after spinal cord injury using a partial body weight support harness to facilitate ambulation. Edgerton and colleagues[67,68] and Barbeau and colleagues[69,70] explicitly derived their therapeutic regimen for human spinal cord injury from their own early work in animals[71,72]. Using a similar methodology, other investigators (for example, Wernig and Müller[73] in people with spinal injury, and Hesse *et al.*[41] in people with stroke) have also relied on basic research in animals in the formulation of their therapeutic procedures. Importantly, new approaches to neurorehabilitation are not restricted solely to the motor system, but also encompass several sensory modalities (BOX 1).

Another new development stems from research in which D-amphetamine was found to improve the recovery of function in rats after either motor cortex or occipital lesions[74]. Of particular interest is the fact that this pharmacological intervention has an effect on recovery primarily when it is used in conjunction with behavioural training[75]. So far, there have been three published studies in which an attempt has been made to use D-amphetamine to improve the rehabilitation of limb movement[76] or language function[77,78] after stroke. Other pharmacological approaches include the administration of methylphenidate to animals and humans, the use of glycine to enhance weight bearing and stepping in spinal cats, α_2-adrenoceptor agonists to help initiate locomotion or increase treadmill speed in animals and humans with spinal cord injuries, serotonergic antagonists to increase weight bearing and treadmill speed in people with spinal injury, and a combination of serotonin and *N*-methyl-D,L-aspartate to enhance ambulatory activity in neonatal rats[75].

These studies are just beginning to unfold; they involve small numbers of patients and do not include control groups, which will be required for this field to mature. But, in conjunction with animal research, these early results are indicative of the promise that this approach holds. Moreover, animal research shows that an effective behavioural method for improving function is an important substrate, so to speak, for the effectiveness of the pharmacological intervention.

There has been a long history of research on the regeneration of neural tissue within the mammalian CNS after neurological injury; the aim has been to allow new, functional synaptic connections of regenerated or transplanted tissue to form and provide a basis for improved function. The work in this area has now entered a promising phase. Here, again, improvements in function that have been observed in animals have arisen largely in connection with the concomitant use of behavioural techniques. The locomotor ability of spinal-cord-injured rats has been improved after the transplantation of spinal cord tissue[79]. Kondziolka and colleagues[80] have transplanted cultured neuronal cells into the brains of patients with basal ganglia stroke. No training was carried out, but the preliminary results were promising. The discovery that undifferentiated stem cells exist in the mature CNS that can, potentially, assume the role of many neuronal cell types after injury opens new vistas in this area.

The effect of enriched environments on the CNS is another area of research that has a long history, but has recently shown the promise of significant practical applications for rehabilitation. Most of the basic animal research has focused on the ways in which environmental enrichment can enhance the development of the immature nervous system[81]. The important work of Ramey and Ramey[82,83] has shown that, starting at an early age, the use of a comprehensively enriched environment can increase IQ by a mean of 15 points in children from disadvantaged homes compared with control children. In the area of rehabilitation, Fischer and Peduzzi[84] have shown that enriching the environment of rats with novel objects and pathways can substantially improve hindlimb function after spinal cord injury. Moreover, Mattson *et al.*[85] found that an enriched environment that allows ample opportunity for exercise and social interaction substantially enhanced the behavioural outcome of grafting of fetal neural tissue after the induction of an ischaemic infarct in rats.

Concluding remarks

It is evident that most of these promising treatments in the fields of rehabilitation and remediation emerge from behavioural research or research in neuroscience and behaviour, involve behavioural techniques in conjunction with other types of intervention, or make use of behavioural methods to produce an advantageous effect on the CNS. These considerations point to the fact that behaviour can have a profound influence on the function and organization of the nervous system, and that this effect can be manipulated to therapeutic advantage in individuals with CNS injury. The approaches we have described here are not entirely new, but their explicit formulation and the effectiveness with which they are now being applied to humans are without precedent in this field. It is this development that we feel justifies our prediction of an impending paradigm shift in neurorehabilitation.

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