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Theoretical aspects of sensory substitution and of neurotransmission-related reorganization in spinal cord injury

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Spinal cord rehabilitation has progressed enormously since World War II, and persons with spinal cord injuries now have long life expectancies. Research has recently concentrated on improvement of the quality of life, and on neural mechanisms of recovery. This article will explore some aspects of both of these areas. In the first section, the potential applications of sensory substitution systems for such functions as sex sensation and sensation from feet and from robotic hands will be examined. In the second section, the potential role of nonsynaptic diffusion neurotransmission (NDN) in neural reorganization after spinal cord injury will be considered. This article includes portions of previous publications and reports.

Keywords: incomplete SCI; neurotransmission; plasticity; robotic hand; sex sensation; rehabilitation

Sensory substitution

Background

For the brain to correctly interpret information from devices, it is not necessary that it be presented in the same form as in natural sensory information systems. We do not **SEE** with the eyes;[1] the visual image does not go beyond the retina, where it is turned into patterns of pulses along nerves. Those individual pulses are not different from the pulses from the big toe. It is the *brain* which recreates the image from the patterns of pulses. We have previously demonstrated that the brain is able to recreate 'visual' images that originate in an artificial receptor (a TV camera), which are transduced into a tactile display (the TVSS system), and carried to the brain via tactile nerve pathways.[1] Thus, it is only necessary to present the information from a device in a form of energy that can be mediated by the receptors at the man-machine interface, and for the brain, through a motor system (eg a head-mounted camera under the motor control of the neck muscles, for blind persons), to know the origin of the information.

We have previously developed tactile vision substitution systems (TVSS) to deliver visual information to the brain via arrays of stimulators in contact with the skin of one of several parts of the body (abdomen, back, thigh, finger-tip). Optical images picked up by a TV camera are transduced into a form of energy (vibratory or direct electrical stimulation) that can be mediated by the skin receptors. The visual information reaches the perceptual levels for analysis and interpretation via somatosensory pathways and structures.

After sufficient training with the TVSS, our blind subjects reported experiencing the images in space, instead of on the skin. They learned to make perceptual judgments using visual means of analysis, such as perspective, parallax, looming and zooming, and depth judgments. Our studies with the TVSS have been extensively described.[1–10]

After training, our blind subjects using the TVSS system did not feel anything on the skin on which the interface was placed; rather they perceived it out in three dimensional space if they controlled the camera movement. Although the TVSS systems have only had between 100 and 1032 point arrays, the low resolution has been sufficient to perform complex perception and 'eye'-hand coordination tasks. These have included facial recognition, accurate judgment of speed and direction of a rolling ball with over 95% accuracy in batting the ball as it rolls over a table edge, and complex inspection-assembly tasks. The latter were performed on an electronics company assembly line with a 100 point vibrotactile array clipped to the work-bench against which the blind worker pressed the skin of his abdomen, and through which information from a TV camera substituting for the ocular piece of a dissection microscope was delivered to the man-machine interface.[5] In these cases, the stimulus arrays presented only black-white information, with no gray scale.

The skin interface systems we have used previously have allowed us to demonstrate the

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principle, but have had practical problems. We have recently developed a tongue interface that overcomes many of these and may offer the opportunity to develop practical devices.[8,9] The tongue is very sensitive and highly mobile, and lacks the protective outer layer of skin that, for our purposes, acts as an insulator and thus requires electrotactile sensory substitution to have high voltages. The presence of an electrolytic solution, saliva, assures good electrical contact. The results obtained with a small electrotactile array developed for a study of form perception with a finger tip[8] demonstrated that perception with electrical stimulation of the tongue is better than with finger-tip electrotactile stimulation, and the tongue requires only about 3% (5–15 V) of the voltage, and much less current (0.4–2.0 mA), than the finger-tip. The electrode array for the initial tongue studies consisted of a 7×7 array of 0.89-mm diameter, flat-topped stainless steel electrode 'pins', each surrounded by a 2.36-mm diameter air gap insulator. A flat stainless steel plate coplanar with the electrode pins served as the return current path. The electrodes were arranged on a square grid with 2.54 mm interelectrode spacing. The electronic system has been described elsewhere.[3] The present version, a 12×12 array with a more simple electrode geometry, and larger arrays are planned.

The tactile system is as capable as the visual and auditory systems for information transmission,[1] but it has largely been ignored. The tongue display does not require that 'feeling' be altered; the tongue system will carry information from a variety of devices that have nothing to do with feeling.

Orthodontic retainers from a cross-section of orthodontic patients were examined to determine the dimensions of compartments that could be created during the molding process to accommodate the FM receiver, the electrotactile display, the microelectronics package, and the battery. The dimensions and location of compartments that could be built into an orthodontic retainer have been determined. For all the retainers of adolescent and adult persons examined, except for those with the most narrow palates, the following dimensions are applicable: in the anterior part of the retainer, a space of 23×15 mm, by 2 mm deep is available. Two posterior compartments could each be 12×9 mm, and up to 4 mm deep.[8] Knowledge of these dimensions allows the development of a standard components package that could be snapped into individually molded retainers, in which the wire dental clips would also be the FM antenna.

The advantages of dealing with a multi-parameter stimulus waveform, to partially compensate for the low punctate resolution of the tongue display, have not yet been explored in the tongue studies. Although six parameters can be identified – namely, the current level, the pulse width, the interval between pulses, the number of pulses in a burst, the burst interval, and the frame rate – only the level of the current was varied in previous studies. All six parameters in the waveforms can, in principle, be varied independently within certain ranges, and may elicit potentially distinct responses.

In a study of electrical stimulation of the skin of the abdomen, it was found[11] that the best way to encode information with a multidimensional stimulus waveform was through modulation of the energy delivered by the stimulus, which was perceived as a variation of the stimulus intensity. In that case, the energy was varied in such a way that the displacement in the parameter space, corresponding to a given transition between energy levels, was minimal (gradient mode of stimulation). Although the gradient mode of stimulation[11] requires a real-time fulfillment of mathematical constraints among the variations of all the parameters, its implementation could be included within the microelectronic package for signal treatment. The methods tested for the abdomen may prove their efficacy in the stimulation of the tongue as well, especially when more sophisticated and meaningful patterns are to be displayed onto higher resolution electrode arrays.

The goal is to develop man-machine interface systems that are practical and cosmetically acceptable. For blind persons, a miniature TV camera, the microelectronic package for signal treatment, the optical and zoom systems, the battery power system, and an FM-type radio signal system to transmit the modified image wirelessly will be included in a glasses frame. For the mouth, an electrotactile display, a microelectronics package, a battery compartment and the FM receiver will be built into a dental retainer. The stimulator array could be a sheet of electrotactile stimulators of approximately 27×27 mm.

For all applications, the mouth display system would be the same, but the source of the information to be delivered to the brain through the man-machine interface would determine the sensor instrumentation for each application. Thus, as examples, for hand amputees, the source would be sensors on the surface of the hand prosthesis, for astronauts, the source would be sensors on the surface of the astronaut glove, for night vision the source would be similar to the glasses system for blind persons but would have an infra-red camera, and for pilots and race car drivers whose primary goal is to avoid the retinal delay (greater than the signal transduction delay through the tactile system) in the reception of information requiring very fast responses, the source would be built into devices attached to the automobile or airplane. Robotics, and underwater exploration systems would require other instrumentation configurations, each with wireless transmission to the mouth display. For spinal cord injured persons, two systems, for sex sensation and for sensation in a robotic hand, will be discussed below.

Persons who had lost hand sensation due to Leprosy have been able, with the use of an

instrumented glove with the sensory information delivered to a sensate area (forehead), to 'feel' objects that they touched. This is relevant to the development of robotic hands for persons with high quadriplegia, discussed below. Under NASA sponsorship, we extended this work to the development of gloves for astronauts. Sensors were placed in the fingertips of gloves, in order to compensate for the loss of tactile sensation that causes the decrease in manual performance.[12]

In a related project, an insole-pressure pad receptor system was developed by Professors Wertsch and Harris (Marquette U., Milwaukee, USA), and Bach-y-Rita and Webster (U.W.-Madison, USA), for studies with sensory substitution, and for diabetic persons with insensate.[13–16] The pressure data acquisition system developed consisted of a pair of insoles instrumented with 14 pressure sensors, a portable microprocessor-based data acquisition system, and a microcomputer. This might lead to a system for sensory information from the feet delivered to a tongue display for persons with low level paraplegia. Such information would be helpful in ambulation on uneven terrain, and could also signal weight shifts. It is possible that proprioceptive information could also be delivered to the tongue display.

Sex sensation

A project has been designed to develop a tactile sensory system, consisting of an instrumented penile sheath and a wireless connection to an array of electrotactile tongue stimulators built into a dental orthodontic retainer, to provide sexual sensation for spinal cord injured men and women (for whom the penile sheath will be worn by her partner).

Decrease in sexual function after a spinal cord injury is a major cause of decreased quality of life for both men and women. Treatment of sexual dysfunction in the SCI population has focused on the restoration of erectile function.[17] With the various treatments that include implants, intracavernous pharmacology and vacuum erection devices, it is possible to restore satisfactory erectile function to most spinal cord injured men.[18] However, sensation is impaired in the vast majority of the SCI population, which Lloyd and Brown[18] consider to be ' . . . much more difficult to treat'.

Loss of orgasm appears to be the major SCI sexual problem. The loss is mainly due to loss of sensation. Women with complete loss of vaginal sensation can reach orgasm by caressing of other parts of the body that have intact sensibility for touch (for instance the ear-lobes and the nipples) and some men can be taught to achieve orgasm – not to be confused with ejaculation – from comparable caressing (Fugl-Meyer, personal communication). He noted 'There is to our knowledge, however, no technique available to re-establish or substitute penile sensibility in these patients. And such sensibility is, for most men, prerequisite for reaching orgasm'. He further wrote: 'To us, a subject who perceives that she or he has reached an orgasm has an orgasm, as the orgasm really occurs in the brain and not in the genitals'.

Experience with tactile sensory substitution, reported above, has led to the hypothesis that a sensory penile sheath and tongue display will provide the opportunity, with training, to have the sensation of sexual organ stimulation. Comparably, a blind person using a long cane to locate a break in the sidewalk pavement perceives the break at the tip of his cane, not in the hand, even though the sensory receptors are located in the hand holding the cane, and a person with lost hand sensation due to Leprosy located the sensation to the gloved hand containing artificial sensors, even though the electrotactile display activated receptors on the forehead (*cf*,[5]). One of our Leprosy subjects, after only 2 days of training, reported the wonderful sensation of touching his wife, which he had been unable to experience for 20 years.

Robotic hand sensation

It appears possible to develop a tactile feedback system for a functional robotic prosthesis for persons with high-level quadriplegia that provides meaningful information about object shape and orientation in the end-effector. The ultimate representation of this system will consist of high-resolution tactile sensors built into the tips of the end-effector, a three-fingered nine degree-of-freedom (DOF) robotic hand, and the self-contained intra-oral microelectronic package having signal treatment, battery, FM radio link, and electrotactile tongue display fitted into an individually molded dental retainer. The tactile feedback would contain information about shape, shear forces, pressure distribution, slip, etc, enabling a person with high-level quadriplegia to literally feel the object being manipulated.

The system for spinal cord injured persons should have the ability to control the type of input signal to create a more sophisticated stimulation pattern, allowing for the addition of a greater variety of possible sensation qualities (or 'electrotactile colors'[19]) to the stimulus, as recent studies from our research group have demonstrated.

There has been significant work in developing prostheses controlled by people with high-level quadriplegia or amputation that rely primarily on visual feedback. Experience from tele-operation research has demonstrated that remote robotic manipulation control is vastly enhanced when augmented with sensory feedback of contact information between the manipulator and the object (contact, force, and other tactile information). The majority of research in robotics, tele-surgery, and virtual reality is in developing feedback to the operators' fingers – thus producing systems with limited utility in rehabilitation medicine.

In tele-operation, a human operator remotely controls a robot in a hazardous or inaccessible environment. These systems have been used for years in the nuclear industry and for undersea exploration, but present systems are slow and clumsy, primarily due to the lack of appropriate sensory feedback to the operator. In early systems visual feedback was the only sensory information available. The tele-manipulation community has long understood the need for haptic information for manipulation, prompting significant research in robotics and virtual reality communities.[20,21] Tactile 'events' (contact, grasp force, slip, etc.) convey information about the state of the hand-object system that is essential for robust control of manipulation. Research on haptic interfaces (force and tactile feedback) has demonstrated that tactile feedback permits remote execution of tasks that are otherwise impossible with previous technology.

Tactual feedback systems typically present force or vibration information to the operator. Force reflection systems, such as the Phantom (Sensible Technologies), exerts an external force on the user's fingertip – creating the illusion of interactions with solid virtual objects. Smooth spheres, flat walls, and sharp corners can be convincingly conveyed to the human haptic system using such devices. Other systems convey vibrations from the remote robot's end-effector. Howe[22] demonstrated that that vibratory information can signal important events such as the first instant of contact and the onset of slip. Howe[22] showed that conveying slip information from the remote robot to the operator's fingers triggers a physiological slip reflex, providing automatic and unconscious regulation of grasp force.

To date, the majority of the systems are designed to provide feedback to the operator's hands via special displays or gloves in order to stimulate the 'normal' manipulation feedback channels that the operator would utilize if he/she were handling an object directly. Some research groups[23] have developed mechanical devices to stimulate the mechanical receptors in the hand. These devices are fragile, consume large amounts of power and generally are not portable. Others have developed electrotactile and vibrotactile displays (*cf*,[7]).

Since sensation is lost together with motor control below the level of the spinal cord injury, sensory information from the robotic hand must be delivered above the level of the lesion. The tongue display is thus feasible for persons with high quadriplegia, and offers the possibility of useful robotic hand control.

Nonsynaptic diffusion neurotransmission

Background

Nonsynaptic diffusion neurotransmission (NDN) has emerged as a mechanism of information transmission that may play multiple roles in the brain, including normal and abnormal activity, brain plasticity and drug actions.[5,24]

NDN, also called volume transmission[25] includes the diffusion through the extracellular fluid of neurotransmitters released at points that may be remote from the target cells, with the resulting activation of extrasynaptic receptors, as well as intrasynaptic receptors reached by diffusion into the synaptic cleft. NDN also includes the diffusion of substances such as nitric oxide (NO) and carbon monoxide (CO) through both the extracellular fluid and cellular membranes.

NDN may play a role in learning. The demonstration by Bonhoeffer, Staiger and Aertsen[26] of spreading potentiation, extended by Schuman and Madison,[27] strongly suggests that a principal mechanism of brain plasticity (long-term potentiation; LTP) involves both selective synaptic changes as well as distributed potentiation by means of diffusion to nearby cells. A 'News' report 'Learning by Diffusion . . . in SCIENCE has called attention to this mechanism.[28]

Early studies on regional distribution of enkephalin in the brain pointed out discrepancies, or 'mismatches', between opiate peptide distributions and opiate receptors, such as those between dense enkephalin-containing terminals and sparse opiate receptors.[29] These were initially considered to be exceptional instances. However, Herkenham[30] has reviewed the evidence for mismatches for a number of neurotransmitters, including peptides, monoamines and amino acids, and he concluded that, in the brain, mismatches are the rule rather than the exception. Studies in the laboratory of Basbaum have demonstrated that mismatches in the substance P receptors and sites of release (only 15% synaptic opposition was noted) has been interpreted, in the presence of electron microscopic evidence of widespread (70%) coverage of the cell surface by substance P receptors, as supporting the conclusion that 'much of the surface of substance P receptor-expressing neurons can be targeted by substance P that diffuses a considerable distance from its site of release'.[31]

Studies on the extracellular space, calculating the diffusion of ions in the brain-stem microenvironment in the living brain,[32,33] confirm the conclusions of van Harreveld[34] and others that about 20% of brain tissue is extracellular space. Furthermore, work carried out in Routtenberg's laboratory in the late 1960s demonstrated that transmitters could readily move in the extracellular space (*cf*,[35]), and microdialysis studies indicate that virtually all the neurotransmitters are found in the extracellular fluid,[36,37] which confirms that the conditions exist for NDN.

Glial cells may play a role in NDN, but it is not evident in studies to date. Neurons and glia are separated by narrow, fluid-filled spaces that are about 20 mm wide and prevent nerve impulses from spreading into glial cells. Neurons transmit signals into glial cells by releasing potassium into the intercellular spaces. Glial cells do not have axons,

but they have processes (at times less than 1 micron thick) which means they are physically close to neurons and to other glial cells. Glial cells have many gap junctions connecting them to other glial cells, but gap junctions were not seen between neurons and glia.[38] Fróes and Campos de Carvalho[39] have reviewed the recent evidence for the existence of gap junctions between neurons and glia, and conclude that ' . . . the gap junction-mediated interplay of glial and neuronal networks may be transitory and possibly limited to earlier stages of CNS histogenesis'. It is possible that some of the evidence put forward as supporting gap junctions between glia and neurons may reflect unrecognized NDN information transfer.

There is strong evidence from many sources that information transmission in the brain occurs by many means in addition to the classically-recognized axonal transmission. Fróes and Campos de Carvalho[39] reviewed the evidence for astrocytic gap junctions serving as the basis of long-range glial signaling pathways, and in addition to NDN (discussed above and below), we have suggested that activity-related neuronal threshold changes accompanying changes in the volume fraction (the space between neurons) may serve as a biophysical informational pathway.[40] However, much work remains to be done to clarify the existence and the functional roles of mechanisms of extrasynaptic transmission.

The comparative efficiency of diffusion and 'wiring' (synaptic) transmission has been discussed in regard to the mass, sustained activity with which the locus coeruleus is associated.[41] The coerulean system can activate over a long period of time at a relatively low energy cost: the varicosities are generally not part of a junction, and so release of noradrenaline must take time to diffuse through the extracellular fluid to extrasynaptic receptors. Activity induced in the distant dendritic tree takes considerable time to reach the soma, where the influence is maintained over a period of time. In the absence of a junction, inactivation of the noradrenaline is slowed: the synapse has a full panoply of degradation enzymes and re-uptake mechanisms, while non-junctional receptor sites possess few if any of these inactivating devices. Glial mechanisms provide still another mechanism for affecting the time course of noradrenaline activation. We concluded therefore, that the effect of non-junctional noradrenaline is likely to be both more massive and longer lasting than a similar quantity of noradrenaline released at a synapse.[41] We have calculated the space[42] and energy (Aiello and Bach-y-Rita, in preparation) considerations in synaptic and nonsynaptic neurotransmission and have determined that it is very unlikely that synaptic neurotransmission could be the exclusive means of information transmission in the brain.

NDN may be the primary information transmission mechanism in certain mass, sustained functions, such as sleep, vigilance, hunger, brain tone and mood[42] and certain responses to sensory stimuli, as well as several abnormal functions, such as mood disorders, spinal shock, spasticity, shoulder-hand and autonomic dysreflexia syndromes, and drug addiction.[5,43,44]

In view of Herkenham's findings that receptor-release-site mismatches (in comparison to synapses, at which they are in close opposition) are the rule rather than the exception,[29,30] synaptic transmission may not be quantitatively the principal means of neurotransmission in the brain. Even before the era of molecular biology, the exclusivity of the synapse as a means of transmitting information had been questioned, when results obtained from intra- and extracellular microelectrode studies of polysensory brain stem neurons could not be fitted into the prevailing connectionistic theory of brain function.[45] I interpreted the results as suggesting the presence of diffusion neurotransmission.

Following their demonstration of neurotransmitter-filled varicosities distant from synapses, Descarries and Beaudet[46] suggested that the biogenic amines released from non-synaptic varicosities may act not only upon adjacent post-synaptic surfaces, but also in tissue of more distant receptor elements. More recent studies have confirmed and extended those findings: (*cf,*[47–49]). These and other early diffusion neurotransmission studies, by Fuxe, Routtenberg, Vizi, and others, have been summarized.[5,25]

Individual movements or functions, such as playing the piano, or watching a tennis game, require great selectivity, rapid initiation and rapid ending; for such functions, synaptic action is essential. However, for mass sustained functions (eg, sleep, mood, hunger), sustained, widespread activity (rather than speed and selectivity) is required, which appear to be largely mediated by NDN.[5,42] Many functions may be produced by combinations of both types of neurotransmission. In the piano playing example presented above, in addition to the relevant synaptic mechanisms, the finger movements can be more precise in the presence of adequate preparation including changes in brain tone (probably mediated by noradrenaline), and the visual perception of the tennis game may require neuronal receptivity to be set at a high level, probably involving several neurotransmitters, including nitric oxide[50] and dopamine[51] in the retina, serotonin and histamine in the lateral geniculate nucleus[52,53] and noradrenaline in the visual cortex.[54] These effects appear to be primarily non-synaptically mediated. Some of them have been called modulation; the modulation of synaptic activity by diffusion outside the synaptic gap is also a nonsynaptic, diffusion-mediated activity.

NDN can be modeled by students in a university classroom,[55] who can be equated to neurotransmitter molecules in a vesicle. Upon release, they must go to specific other classrooms spread throughout the campus (receptor sites). They flow out into the halls and the grounds between buildings (extracellular fluid), where they mix with other students (neurotransmitter molecules) from other classrooms (vesicles) going to other target classrooms. They walk (diffuse)

to their specific classrooms (receptors) which they enter (bind). In contrast, 'synaptic transmission' students would be propelled along enclosed walkways connecting each point-of-origin classroom with the target classroom.

The pharmacology of recovery from central nervous system damage, although in its infancy, holds enormous promise. NDN may play a role in the actions of neuroactive drugs, many of which may not act primarily on synapses, although only synaptic action is usually considered. For example, Barondes[56] discussed the changes in psychiatric practice that have occurred with the widespread use of Prozac, and he commented on its possible mechanisms of action, which were considered strictly in terms of synaptic information transmisson. However, serotonin, which Barondes[56] pointed out is involved in the action of Prozac, is among the most highly nonsynaptic monoamines in the central nervous system (*cf*,[57]).

Thus, other than the conceptual limitations imposed by the present synaptic-dominated model of brain function; there is no reason to consider that Prozac or any of the drugs used in psychopharmacology, operate exclusively via synaptic mechanisms.[54] In fact, accumulating evidence suggests the contrary (*cf*,[5,58]); the primary mechanisms may be by NDN.

Within the context of the above discussion of NDN, this should not be a surprise. Mood is a mass sustained function;[42] it is more comparable to hunger, pain and sleep than it is to visual perception and fine motor movements, which require synaptic activity (but which also have important NDN components at all levels (*cf*,[5]). Thus disorders of mood (and other psychiatric disorders) may be disorders of NDN mechanisms.

Vizi[59–62] noted that drugs have difficulty reaching the receptors intrasynaptically. He noted that the sensitivity of nonsynaptic receptors is higher, and they are much more accessible to drugs. Receptors located presynaptically or prejunctionally (and thus, by definition, outside of the synaptic cleft) must be reached by means of diffusion through the extracellular fluid. Vizi suggested that diffusion neurotransmission may be the primary means of activation of receptors by externally applied or administered drugs.

Thus, concepts of the effects of drugs on the central nervous system have progressed from a consideration of the effects of specific agents on 'the brain', to a consideration of their differential effects on specific regions of the brain (eg,[63]), to an understanding of their effects on specific neurotransmitter systems, to knowledge of their specific intra- and extra-cellular mechanisms. The addition of an understanding of the mechanisms of transport within the brain and activation of synaptic and extra-synaptic receptors (as well as intracellular activation following diffusion across membranes, such as by NO; Snyder has referred to NO as 'one of the main neurotransmitters in the brain'[64]) should aid in the development and in the evaluation of the mechanisms of action of effective neuroactive drugs.

Many brain functions appear to be controlled by cell-assemblies of varying numbers and populations of neurons. An individual cell may participate in various assemblies, much like the participation in various committees of an individual person. Tononi and Edelman[64] predicted that ' . . . during cognitive activities involving consciousness, there should be evidence for a large but distinct set of distributed neuronal groups that interact over . . . (hundreds of milliseconds) much more strongly among themselves than with the rest of the brain'. They cited evidence that in working memory tasks, sustained neural activity is found in the prefrontal cortex. NDN may play an important role in these mass, sustained functions, which may involve those brain areas that are highly developed in humans.

Cell-assembly architecture for mass, sustained functions is likely to consist of varying combinations of synaptic and NDN connectivity, depending on the specificity of the function. The unrealistic figures resulting from hardwired connectivity calculations,[55] and the space and energy saving functional roles of the extracellular space in NDN,[40] support Tononi and Edelman's considerations. This is compatible with a proposed law of the conservation of space and energy in the brain.[66]

The energy and space considerations of the mass, sustained mechanisms considered by Tononi and Edelman also relate to the interest in brain energetics (eg[67]) by Physical Anthropologists considering '. . . the possibility of energetic constraints on evolution';[68] it was noted that the human brain and body do not use more energy than smaller-brained animals of similar size. I propose that human functions such as the cognitive activities involving consciousness studied by Tononi and Edelman, and the parts of the human brain (such as the pre-frontal cortex) that show the greatest size increase over other animals, may be exactly those functions and structures in which space-and-energy-expensive synaptic neurotransmission is largely replaced by NDN.

NDN mechanisms appear to be involved in both plastic changes of learning and reorganization following brain damage, as discussed elsewhere (*cf*,[5]). These include those related to up- and down-regulation of synaptic as well as extrasynaptic receptors, such as those noted by Westeberg *et al*[69] in a rat model of transient cerebral ischemia. One of the few related human studies demonstrated that, following the destruction of the ascending dopamine pathways by a unilateral human brain stem stroke, there is an up-regulation of dopamine receptors in the denervated hemisphere.[70] This type of response is difficult to study in the brain, but as has been the case with many other mechanisms, the neuromuscular model may offer insights. When a muscle fiber is denervated, there follows a massive up-regulation of receptors on the entire cell membrane, resulting in hypersensitivity to

low concentrations of acetylcholine.[71] If up-regulation of specific receptors has occurred following brain damage resulting in partial or total denervation (comparable to the massive up-regulation on the cellular membrane of denervated muscle), those cells may similarly become hypersensitive to specific neuroactive substances, and thus respond to the low concentrations of those substances in the extracellular fluid.

When diffusion neurotransmisson was first considered in 1964,[45] very few neurotransmitters had been identified. At present, there are dozens known ('neurotransmitter' is defined broadly in this paper, as noted in[5]). Furthermore, many neurotransmitters have up to dozens of sub-types of receptors identified. It is difficult to imagine how a fully synaptically-connected brain could make use of so many specific receptor sub-types, but it does form the substrate for selective diffusion neurotransmission. All of the neurotransmitters may be found in the extracellular fluid, and a particular cell may communicate with a distant cell by the release of a very specific form of a transmitter, which would be bound by the very specific sub-type of a receptor in the distant cell.

NDN mechanisms in the spinal cord

There is evidence that the noradrenergic[72] and serotonergic[73] and partly dopaminergic[48] neurotransmission in the dorsal horn is principally nonsynaptic. Some systems in the spinal cord may be highly nonsynaptic. Maxwell *et al*[73] noted that in the marginal zone of the dorsal horn (Rexed lamina I), serotonergic innervation is only 3.85% synaptic, and they suggest that the transmitter is released in the extracellular space. They discussed their findings in regard to the role of the descending serotonergic systems in analgesia. Marlier *et al*[74] also calculated a non-corrected synaptic incidence, while Rajaofetra *et al*[72] and Ridet *et al*[49] have determined the synaptic incidence of serotonergic, noradrenergic and dopaminergic innervation of the spinal cord by two procedures: by counting synapses on single sections and then applying the correcting formula established by Beaudet and Sotelo,[75] and by counting synapses on serial ultrathin sections. All of these studies reveal a high nonsynaptic incidence.

Bach-y-Rita and Illis[76] discussed the recovery of reflexes in spinal shock in the context of the possible up-regulation of receptors in the synapses and on the surface of the partially denervated spinal cord cells, resulting in the increased sensitivity to neurotransmitters and other neuroactive substances released at the surviving synapses or transported in the extracellular fluid (diffusion transmission). Although the neurological syndrome may be primarily motor such as paralyzed limbs, the effect on the central nervous system of the deficit of sensory information is critical,[76] and thus is highly suggestive of a role for NDN in spinal shock.

It is probable that there are a comparable number of NDN mechanisms in the spinal cord to those found in the brain. The up- and down-regulation of extrasynaptic receptors probably plays a role in the functional reorganization that follows spinal cord injury. The intriguing possibilities this presents for appropriate rehabilitation, possibly combined with appropriate targeted medications, remain to be explored. Furthermore, some very unusual cases of recovery should be re-examined in the light of these and other findings.

Conceptual rigidity has severely limited recovery obtained following brain or spinal cord injury. This has been extensively discussed elsewhere.[5] The dominance of a localizationist, hard-wired concept of the central nervous system has largely excluded reorganization-based functional recovery, and thus even the field of Rehabilitation Medicine has often aimed primarily at adjustment to the loss rather than the recovery of function. Our clinical experience has shown that if the rehabilitation goals, the attitudes of the Therapists and the mental preparation of the patients are oriented towards early and late recovery of function, very significant recovery can be obtained, even many years after the damage.[5,77–79]

Many years ago at a meeting in Koln, a distinguished scientist reported a fascinating case of recovery after the destruction of almost the entire spinal cord (confirmed at autopsy following a second accident). I included it as an anecdotal report in my chapter in the Proceedings of that conference.[80] No firm conclusions can be drawn from it, but it is reproduced below because of the implications for recovery in incomplete spinal cord injury, based on massive reorganization, probably including NDN mechanisms discussed above:

> 'Theodore Rasmussen (personal Communication) discussed the unpublished case of a man who became paraplegic following an automobile accident, but gradually regained complete function and was able to enlist in the US Navy. He served three enlistment periods with no physical limitations. He died in a second automobile accident. Autopsy revealed that a complete (approximately 1 cm) separation of the spinal cord at the level of T7 had resulted from the first accident. However, microscopic study revealed approximately 150 axon cylinders embedded in the fibrous tissue separating the two portions of the spinal cord. Thus, it is likely that recovery was obtained by functional reorganization of the input to the cell bodies of the 150 remaining fibers, as well as the possible redirection of axon terminals'.[80]

If the spinal cord injured person discussed in this anecdotal report really was able to recover very significant function with only a bridge of a small number of surviving fibers joining the spinal cord proximal and distal to the lesion, it would indicate

that there was very extensive reorganization below the lesion, with the remaining fibers carrying very complex information and interacting with many cells below the lesion. It merits the development of an experimental model, which is presently being planned.

Anecdotal and unusual case reports can often provide clues to mechanisms that have been overlooked in standard science. A previous such report, of unusual recovery from a major stroke in a person of advanced age, with autopsy evidence of the large lesions,[80] led to the evaluation of the remarkable home rehabilitation program. This has been a source of material for developing our present late rehabilitation methods.[5,77,81]

The early and late rehabilitation programs, psychosocial issues and the attitudes of the therapists play a very important role in recovery. However, it is beyond the scope of this article to examine these issues in detail; they have been extensively published elsewhere (*cf*,[5,77,79]). Attention to these factors has led to interesting early and late recovery of function not only in brain damaged persons, but in persons with incomplete spinal cord injuries, although these have not yet been systematically studied.

Implications for spinal cord injured persons

This paper has explored several areas that have emerged from experimental evidence and theoretical reasoning within a broad conceptual framework. Further laboratory and clinical research, and rehabilitation (including engineering) research and development, may bring some of these into practicality and lead to improved functional recovery and quality of life for persons with spinal cord injuries.

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