Neural Plasticity: For Good and Bad

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The brain’s ability to change its organization and function is necessary for normal development of the nervous system and it makes it possible to adapt to changing demands but it can also cause disorders when going awry. This property, known as neural plasticity, is only evident when induced, very much like genes. Plastic changes may be programmed and providing a “midcourse correction” during childhood development. If that is not executed in the normal way severe developmental disorders such as autism may result.

Normal development of functions and anatomical organization of the brain and the spinal cord depend on appropriate sensory stimulation and motor activations. So-called enriched sensory environments have been shown to be beneficial for cognitive development and enriched acoustic environment may even slow the progression of age-related hearing loss. It is possible that the beneficial effect of physical exercise is achieved through activation of neural plasticity.

The beneficial effect of training after trauma to the brain or spinal cord is mainly achieved through shifting functions from damaged brain area to other parts of the central nervous system and adapting these parts to take over the functions that are lost. This is accomplished through activation of neural plasticity. Plastic changes can also be harmful and cause symptoms and signs of disorders such as some forms of chronic pain (central neuropathic pain) and severe tinnitus. We will call such disorders “plasticity disorders”.

§1. Introduction

Neural plasticity is a property of the nervous system that only becomes apparent when expressed similar to genes, which only become apparent when expressed (or activated). Activation of neural plasticity has similarities with learning and arousal.

Activation of neural plasticity occurs normally during the first years of life and provides a “midcourse correction” of the function of the nervous system. If this does not occur properly developmental disorders become the result. During life, the effects of activation of neural plasticity can be beneficial to the individuals in the way it can make the nervous system adapt to different demands. Activation of neural plasticity can also be harmful in that it can cause symptoms of disorders such as chronic pain and tinnitus.

In this paper I will describe what changes occurs in the nervous system as a result of activation of neural plasticity, what can cause activation of neural plasticity and what the consequences of the changes can be. I will discuss the benefit of neural plasticity what happens when neural plasticity become maladapted and results in plasticity disorders. The purposiveness of neural plasticity will be discussed in connection with hypotheses of evolution of neural plasticity.
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§2. How can the nervous system change its function?

Plastic changes comprise changes in the efficacy of synapses (connections between nerve cells), formation of new synapses and elimination of existing synapses. Activation of neural plasticity can eliminate synapses or create new synapses and it may cause nerve cells to die (programmed cell death, PCD). The protein synthesis in nerve cells may change through activation of neural plasticity, thus another form of change caused by expression of neural plasticity.

The efficacy of synapses may be altered; unmasking of dormant synapses and masking of active synapses may occur as a result of activation of neural plasticity. Such changes can cause redirection of the flow of information by blocking active pathways or opening pathways that were blocked before the activation of neural plasticity. Activation of neural plasticity can thereby make information reach other parts of the CNS than those that normally receive such information.

Addition of new synapses also occurs through learning but learning does not involve change in function. The efficacy of synapses also occurs as a result of arousal, but again that does not change the function of the nervous system, as does activation of neural plasticity.

2.1. What controls activation of neural plasticity?

Lack of stimulation of sensory systems (sensory deprivation) is perhaps the strongest factor of those that can activate neural plasticity. Increased activation of specific neural circuits can also induce neural plasticity. The areas of the cerebral cortex that is activated have been shown to increase from such extensive use such as has been observed in individuals who use some of their fingers more than what is normal such as in string players. The portion of the somatosensory cortex that is activated by movements of the fingers that are extensively used expands.

The vestibular ocular reflex that normally ensure a stable image on the retina during head movements by moving the eyes in the opposite direction of the head movement can adapt to situations where people wear different spectacle. It is even possible to adapt to wearing reversing prisms, which reverse the direction of the movement of the image on the retina, thus requiring that the eyes are moved in the same direction as the head (the gain of the vestibular ocular reflex must change from \(-1\) to \(+1\)).

Many other internal and external factors can activate neural plasticity. It has been shown that amputation of a finger, thus deprivation of input from the skin, causes neighboring areas of skin (adjacent fingers) to take up the cortical areas normally representing the skin of the amputated finger.

In sensory systems, deprivation of input is perhaps the strongest promoter of neural plasticity. Internal factors of various kinds may also induce neural plasticity. For example, the morphological changes that occur in disorders such as Alzheimer’s disease may cause activation of neural plasticity. The cause of expression of neural plasticity, however, is often unknown.

Understanding speech through the use of prostheses such as cochlear and brainstem implants is possible because the brain can reorganize through activation of
neural plasticity to properly interpret the neural code provided by these prostheses despite the code is different from that of the messages the ear normally sends to the brain.

Abnormal activity of neurons can induce neural plasticity as proposed by Hebb\(^6\) who showed that simultaneous activation of many neurons can result in establishment of anatomical connections between the neurons (“neurons that fire together wire together”), thus a temporary change in neural activity can cause a permanent structural change.

While the blueprints of the brain are laid out before birth by genetics and epigenetics (genetics that is affected by environmental factors) the brain at birth is not finally developed and a “midcourse correction” is necessary to reach the completion of the development of the brain. In this dramatic revision of the organization of the nervous system many synapses are eliminated and even nerves cells in large numbers are eliminated (PCD). As much as 50% of nerve cells have been reported to die during the change that normally occur early in life.

The changes that normally occur during the first few years after birth are extensive and consist of adjustment of synaptic efficacy, elimination of some synapses (pruning) and creation of new synapses; elimination and creation of connections between cells and extensive cell death (programmed cell death, PCD, also known as apoptosis).

The classical studies by Wiesel and Hubel\(^7\) on the development of the visual system show that the organization of the brain is not rigid and that sensory input is necessary to achieve the normal organization. Another sign of the importance of activation for the organization of the central nervous system regard the normal tonotopic organization of the auditory system that is achieved by stimulation of the cochlea\(^8\) and without that there is only a rudimentary tonotopic organization in the auditory pathways of deaf animals (cats).\(^9\)

It has been shown that cross-modal sensory interaction is normal during this developmental period\(^10\) and that has been taken as a sign that the use of the non-classical ascending auditory pathways\(^11\) is normally reduced during early childhood. Activation of neural plasticity provides this “midcourse correction” of the genetically controlled (Darwinian) development of the nervous system.

§3. Effects of activation of neural plasticity

Activation of neural plasticity can have both beneficial and harmful effects. The beneficial effects have received far more attention than the harmful effects causing disorders of several kinds (plasticity disorders). A form of pain (central neuropathic pain) and ringing in the ears (tinnitus) are the best-known examples of plasticity disorders. Phantom sensations that may occur after damage to peripheral nerves such as occurs for example in connection with leg amputations are other examples of plasticity disorders that are caused by misdirected activation of neural plasticity.\(^12\)

It is possible that these symptoms are caused because of misdirected plastic changes that have attempted to restore the lost functions. Some forms of muscle spasm are also caused by such incorrect activation of neural plasticity. Addiction such as to
narcotics is another kind of disorders that most likely is caused by an (unfortunate) activation of neural plasticity.

3.1. Beneficial effects of activation of neural plasticity

Activation of neural plasticity can help recovery from injuries to the brain. Perhaps the best known effect of activation of neural plasticity is its help in recovery from injuries to the brain from trauma and strokes. Trauma to the head is common and occurs from automobile accidents and other kinds of blow to the head, gunshots and explosions. The injuries may be in the form of lack of oxygen (causing ischemia), structural damage to brain tissue or bleeding.

Ischemic strokes (strokes that are caused by obstruction of a blood vessel) cause permanent damage to specific regions of the brain because of ischemia if the blood supply is not restored within a short time. Hemorrhagic strokes (caused by rupture of a blood vessel) cause widespread damage and often death. Ischemic strokes are by far more frequent than hemorrhagic strokes (about 4 to 1). When a few hours have elapsed after the cessation of blood flow to neural tissue, the function of the tissue cannot recover, and the recovery of functions that may occur is caused by redirection of neural activity to functional parts of the brain that can take over the lost functions directly or more often after changes in the organization of these structures through activation of neural plasticity.

Recovery of functions by re-routing information that has been processed in the damaged parts of the brain to intact parts depends on the availability of intact regions that can perform the functions of the damaged parts of the brain, thus a dependency on redundancy. Not all brain functions have redundancy, however. There is limited redundancy in the control of motor functions. Impairment speech that is exclusively caused by injuries to the left side of the brain cannot be replaced by that of other structures.

Training and exercise is usually the means that are used to promote activation of neural plasticity. More recently it has been tried to stimulate cerebral cortical areas electrically to accelerate recovery.\(^\text{13}\)

Activation of neural plasticity is also important for adaptation to changing demands. Activation of neural plasticity is necessary for the success of prostheses such as cochlear and brainstem implants that are used to restore hearing in deaf individuals.

3.1.1. Activation of neural plasticity can help adapting to changing demands

Advantages from the use of prostheses depends on the ability of the brain to change its function so that it can adapt to the input from sensory prostheses and change the way it control prostheses of limbs. Hearing prostheses (cochlear and brainstem implants) used to treat deafness requires reprogramming of hearing and the use of artificial limbs requires reprogramming of motor control.

3.1.2. Hearing prostheses

Two kinds of hearing prostheses are presently in use for restoring hearing in deaf individuals, namely cochlear implants and brainstem (cochlear nucleus) implants.\(^\text{14}\) The cells in the cochlear nucleus are the targets of auditory nerve fibers.\(^\text{15}\) Cochlear
implants are used in individuals whose deafness is caused by malfunction of the ear (cochlea). While cochlear implants make use of an array of electrodes placed in the inner ear (cochlea) in such a way that the hearing nerve can be activated directly, cochlear nucleus implants use an array of electrodes placed on the surface of the cochlear nucleus, located in brainstem. Cochlear nucleus implants (also known as brainstem implants) are used in individuals whose hearing nerve has been injured.\textsuperscript{16,17} These two kinds of devices both bypasses the normal function of the cochlea that normally separate sounds into bands of frequencies and compress the range of sound intensities before being coded in auditory nerve fibers by help of the sensory cells in the cochlea (hair cells).\textsuperscript{15} Cochlear nucleus implants in addition bypass the auditory nerve and directly activate the nerve cells that are normally the target of auditory nerve fibers.

The signals applied to the implanted electrodes that are placed in the cochlea or on the surface of the cochlear nucleus are electrical impulses that are controlled by the sound that reach a microphone the used wears. A small digital processor worn by the user of the prosthesis processes the signals from the microphone and prepares the signals that are applied to the electrode array in other ways by separating the sound spectrum into 8 to 20 frequency bands and it also compresses the sounds with regard to their intensity.\textsuperscript{14,18} Modern cochlear and cochlear nucleus implants are the most successful of all neural prostheses and excellent examples of how neural plasticity serve the purpose of adaptation to changing demands. These devices can provide speech discrimination and they even permit many individuals to understand speech under less than ideal circumstances such as in a noisy environment and where many people speak at the same time. Some individuals with cochlear or cochlear nucleus implants can use the telephone.

To achieve this degree of speech discrimination the auditory nervous system must adapt to process signals that are applied to the auditory nerve or the cochlear nucleus. These signals are rather different from those the normal ear provides to the nervous system. Normally, the function of the cochlea as a spectrum analyzer has been regarded to be important for discrimination of sounds especially speech sounds and cochlear and cochlear implants processors perform an approximation to the spectrum analysis that normally is performed by the cochlea. Achieving usable speech discrimination through cochlear and cochlear nucleus implants require substantial re-programming of the auditory system of the brain.

Since the brain is more malleable in young individuals the best results are generally obtained when young children are implanted, but many adults can achieve very good results also.\textsuperscript{19} 

3.1.3. Cochlear implants

The first cochlear implants had only one electrode and thus no spectral information was provided.\textsuperscript{20,21} Such implants did not provide speech discrimination but were helpful by providing sound awareness. It was a major improvement when it became technically possible to place several electrodes in the cochlea and having the
electrical impulses that were applied to each electrode pair controlled by the energy in different frequency bands of sound.\(^\text{18}\) The processing of sound in modern cochlear implants has similarities with that developed in the 1930s\(^\text{22}\) and used as a basis for development of analysis-synthesis telephony in early 1950s for the purpose of reducing the bandwidth of speech signals for transmission over long telephone lines such as transoceanic cables, which at that time had very limited bandwidth.\(^\text{23}\) The technique became known as analysis-synthesis telephony. The principles pursued consisted of analyzing the speech signals before sending it over long lines such as oceanic cables and instead sending slowly varying signals that provided information about the speech. At the receiving end, these signals were used for synthesizing speech, which was then transmitted to the receiver using ordinary telephone lines. Several schemes were pursued for such analysis-telephony but the most promising was that of the channel vocoder,\(^\text{23}\) which separated the speech signal in 10-14 spectral bands and measures of the energy in each band were then sent as slowly varying signals.

These slowly varying signals were then used to synthesize the speech at the receiving end of the long lines. These signals required much less bandwidth than what was required for sending the raw speech signals. Analysis-synthesis telephony,\(^\text{23}\) was never realized because advances in technology made it possible to transmit broadband signals, first through satellites and later through fiber optic cables although the development of these techniques had been nearly completed to perfection they were.

For the purpose of designing such systems much research was done regarding how to reduce the bandwidth of speech signals while preserving intelligibility and the results of these studies became important for the development of cochlear implant processors.\(^\text{14,18}\) These studies showed that information about the power spectrum of speech sounds alone is sufficient for speech discrimination.\(^\text{23}\) Theories about frequency discrimination in hearing have concerned both the spectral aspects of sounds (known as place coding because it is related to the place along the basilar mem-
brane of the cochlea) and the temporal aspects (temporal coding). Studies have shown that spectral coding alone and temporal coding alone\cite{themanumber24} is sufficient for speech discrimination.\cite{themanumber25} This means that there is a considerable redundancy in the speech signals as well as in the auditory system with regards to speech discrimination. The success of modern cochlear implants depends on this redundancy and on neural plasticity.

Older types of cochlear implant processors utilized both the temporal and the spectral (place) aspects of sounds\cite{themanumber26} while modern processors use only the (power) spectral properties of sounds.\cite{themanumber18}

The question of how many channels are needed in cochlear implants for good speech discrimination benefited from old studies that were performed in connection with the design of analysis-synthesis telephony.\cite{themanumber18} It is possible to monitor the progress of the adaptation of the central nervous system to processing and interpreting the signals from cochlear implants through recording of auditory evoked potential.\cite{themanumber28} The latency of a specific component of such evoked potentials, known as the P300 (because its normal latency is approximately 300 msec), decreases with age in children with normal hearing. The young brain is more malleable than the adult brain\cite{themanumber29} and studies of the latency of the P300 component of auditory evoked potentials indicate that normalization of the latency of this component in children with cochlear implants is a valid measure of the success of adaptation to the use of cochlear implants (Fig. 2).\cite{themanumber28,themanumber30} As seen, the normalization of the latency depends on the age the children when the implantation is made.
3.1.4. Cochlear nucleus implants

As mentioned above, cochlear nucleus (brainstem) implants provide electrical stimulation of cells in the cochlear nucleus through an array of electrodes placed on the surface of the cochlear nucleus.\(^{16}\) This means that the signals from processor of such implants bypass both the cochlea and the cochlear nucleus. Cochlear nucleus implants have not been in use for as long as cochlear implants and in the beginning when used in patients who had tumors of the hearing and balance nerve they were not nearly as efficient in providing speech discrimination as were cochlear implants. More recently it has been shown that as good results can be obtained in patients with other forms of trauma to the auditory nerve or in children with birth defects that have injured the auditory nerve such as internal auditory atresia where the hearing and balance nerves get strangled because the opening in the bone is too small.\(^{31}\)

It is more difficult to correctly position the electrode array that provides the electrical stimulation on the surface of the cochlear nucleus than the electrodes that are placed in the cochlea for stimulating the auditory nerve. The use of cochlear nucleus implants is therefore a greater challenge in several ways than cochlear implants. Despite these obstacles, some users of cochlear nucleus implants can achieve similar speech discrimination as users of cochlear implants using the same signal processors as used for cochlear implants.\(^{31}\) The success of cochlear nucleus implants is an indication of the power of neural plasticity together with the redundancy of the auditory nervous system that makes it possible.

These are examples where expression of neural plasticity provides a benefit to an individual person. Activation of neural plasticity can also cause changes in the function of the brain that are not beneficial but instead cause symptoms and signs of disease. We will call that “plasticity disorders”.

3.2. Plasticity disorders

Expression of neural plasticity can cause various form of harm if going awry. We will call disorders that are caused by expression of neural plasticity “plasticity disorders”.\(^{32}\) The best-known plasticity disorders that results from misdirected activation of neural plasticity are certain forms of pain (central neuropathic pain)\(^{33}\) and certain forms of severe tinnitus (“ringing in the ears”).\(^{34}\) These two disorders have many similarities.\(^{34}\) Other disorders where expression of neural plasticity plays an important role are muscle spasm and synkinesis (contractions of other muscles than intended).\(^{33}\) Expression of neural plasticity is also involved in creation of spasticity that often occur in connection with spinal cord injuries. Normal development of the nervous system through childhood requires activation of neural plasticity. Some developmental disorders as believed to be caused by activation of neural plasticity going awry. Activation of neural plasticity may also be involved in causing the symptoms of some balance disorders.\(^{33}\)

3.2.1. Central neuropathic pain

Acute pain is caused by activation of a specific kind of receptors (nociceptors) that sends signals to the brain through specific pain pathways in the brain.\(^{33,35}\) Many forms of chronic pain is not caused by such specific activation of pain receptors
Fig. 3. Schematic flow chart for neuropathic pain, showing the normal pathway for neural activity that gives sensations of pain (upper part). Lower part shows the path for normal sensation such as that of touch. It also shows what happens when dormant synapses are unmasked providing an abnormal route from the somatosensory system to pain circuits, which is the basis for allodynia.\(^{32}\)

but is caused by abnormal neural activity in some brain structures the activity of which reach consciousness and causes the sensation of pain, although there is no physical stimulus that elicits the pain. Such pain that is caused by abnormal neural activity in the spinal cord\(^{36}\) and the brain\(^{37}\) is known as central neuropathic pain and activation of neural plasticity is involved in creating the pain (Moller, 2006a). Central neuropathic pain may start from acute pain such as from injuries to nerves on the body but will continue after the input from pain receptors has ceased.

It has been shown that some neural circuits in the dorsal horn (the sensory part) of the spinal cord are re-organized in individuals with some forms of central neuropathic pain. The neural circuits in the dorsal horn can operate permanently in different modes.\(^{36}\)

Another sign of re-organization that occurs in some forms of central neuropathic pain is alldynia, which is the sensation of pain from light touch of the skin. The presence of alldynia that is a sign that somatosensory information has been re-directed to pain circuits in the spinal cord and the brain is also caused by activation of neural plasticity through which stimulation of touch receptors cause neural activity in pain circuits.\(^{33},^{36}\)

These changes in the organization of the spinal cord and the brain are caused by activation of neural plasticity, most likely through changes in synaptic efficacy but changes in protein synthesis and outgrow or elimination of connections between neurons (axons) may also occur.

3.2.2. Tinnitus

Tinnitus is a sensation of sound that is perceived in the absence of physical sounds reaching the ear.\(^{38}\) It is a phantom sound like hallucinations but tinnitus is meaningless sounds whereas hallucinations are voices or music. Hallucinations can be caused by administration of various kinds of drugs and it occurs in connection with some psychiatric disorders such as schizophrenia.
Tinnitus has many forms, from benign weak intermittent sounds similar to noise or tones, to continuous roaring sounds that may be present 24 hours a day and prevent from sleep and intellectual work and such forms of tinnitus may lead to suicide. Severe tinnitus has many similarities with central neuropathic pain. Tinnitus often occurs together with hearing loss, in connection with exposure to loud sounds or it may occur without any other noticeable symptoms. Some disorders such as Ménière’s diseases, vestibular schwannoma and Williams’ disease are accompanied by tinnitus. In this chapter we will discuss the role of expression of neural plasticity in causing tinnitus.

The abnormal neural activity that causes these sensations can be generated in the ear or in the auditory nerve but most often the sensation is caused by neural activity that is generated in the central nervous system without input from the ear, at least for severe forms of tinnitus.

At least some forms of tinnitus have been regarded as misdirected or overdone attempts to increase the sensitivity of the auditory system to compensate for hearing loss. Tinnitus may thus be a result of increased excitability of neurons in the auditory system that make neural circuits self-oscillate and thus produce neural activity that is perceived as sounds.

Some forms of tinnitus are associated with changes in the connections in the brain. There is two parallel ascending auditory pathways, one classical and one non-classical also known as the lemniscal and the extralemniscal pathways. Neurons in the classical auditory pathway only respond to sounds whereas some neurons in the non-classical pathways also respond to stimulation of other sensory systems (polymodal) (see Fig. 4). While studies have shown indications that both these pathways are active in young children, few individuals older than 15 years have indications that sound perception is affected by somatosensory stimulation, thus indications that the non-classical pathways are not active in adults. The tinnitus in some individuals can be affected by stimulation of the somatosensory system, thus indicating that the non-classical pathways have been re-activated as a part of the disorders of tinnitus.

The classical ascending auditory system uses the ventral part of the thalamus, the neurons of which projects mostly to primary auditory cortices while the non-classical (also known as the extralemniscal) system use the dorsal and medial portions of the thalamus, the neurons of which project to secondary and association cortices thus bypassing the primary cortex. Similar connections are present in other sensory systems. Some neurons in the dorsal and medial sensory thalamus project directly to the amygdala, which can explain the presence of affective symptoms such as depression and phonophobia (fear of sounds) in some individuals with severe tinnitus. These parts of the “emotional brain” can also be reached through the classical ascending pathways, but through a long route involving the primary, secondary and association cortices. This is known as the high route (also known as the slow and accurate route); the subcortical route from the medial and dorsal thalamus is known as the low route (fast and dirty).
3.2.3. Spasm and spasticity

Involuntary muscle contractions, often associated with synkinesis (simultaneous contractions of different muscles) often occur when influence on spinal reflexes from the brain are lost such as in spinal cord injuries.

Motor nerves that regenerate after injuries sometimes are associated with spasm and synkinesis. The presence of synkinesis has been explained by the outgrowing nerve fibers not reaching their correct target muscles. However, studies of regeneration of the facial nerve after trauma have shown that the synkinesis can be treated successfully by exercise, thus an indication that it is caused by re-organization of the facial motonucleus, which is likely to have been caused by activation of neural plasticity. Hemifacial spasm, a rare disorder that causes spasm and synkinesis in one side of the face can be cured successfully by moving a blood vessel off the intracranial portion of the facial nerve. It was therefore believed that the symptoms were caused by injury to the facial nerve but studies have shown that the symptoms instead are generated by hyperactivity and re-organization of the facial motonucleus, and there is evidence that these changes in the function of the facial motonucleus are caused by activation of neural plasticity.

3.2.4. Balance disorders

The balance system helps to maintain posture and it moves the eyes during head movements in a direction opposite to the head movement so that the image on the retina remains steady while turning the head. This all normally occurs without causing any awareness. However, disorders and ingestion of certain poisons can make a person become aware of head movements and it may cause symptoms such as vomiting. For that to occur information must be re-routed and it is an example of changes that are similar to for example allostynia. Common disorders of the balance
(vestibular) system are characterized by vertigo (a sensation of the surroundings are spinning), unsteadiness or nausea. There is evidence that some balance disorders such as benign paroxysmal positional nystagmus\textsuperscript{43} are caused by pathologies of the inner ear whereas other balance disorders such as disabling positional vertigo (a feeling that any head movement cause nausea)\textsuperscript{44} involves re-routing of information from the balance (vestibular) receptors in the inner ear to regions of the brain other than those that are the normal targets for such information, thus signs of activation of neural plasticity.\textsuperscript{33}

There are also indications that neural plasticity is involved in at least one or more of the symptoms of Ménière’s disease. Ménière’s disease is defined as a triad of symptoms: fluctuating hearing loss, tinnitus and vertigo.\textsuperscript{45} It has been assumed that these symptoms were caused by an imbalance of the pressure (or rather the volumes) of the fluid in the inner ear.\textsuperscript{46} It is not known what causes this imbalance but the finding that the symptoms can be ameliorated by stimulation by air puffs applied to the inner ear\textsuperscript{47} points towards functional causes thus possible involvement of neural plasticity.\textsuperscript{33}

There are also signs that activation of neural plasticity may be involved in causing disorders such as age-related hearing deficits,\textsuperscript{48} which were earlier assumed to be caused exclusively by degeneration of sensory cells in the cochlea (mostly outer hair cells). It has been shown that the degree of hearing loss that exposure to loud sounds causes can be affected (decreased) by exposure to less loud sound done before the exposure to loud sound that cause hearing loss.\textsuperscript{49,50} It has earlier been assumed that the cause of age related hearing loss, and hearing loss from exposure to loud sounds was destruction of sensory cells in the cochlea (hair cells). The fact that the hair cells are under control from the central nervous system\textsuperscript{15} may explain how expression of neural plasticity may affect the impairment or deaths of hair cells.

These examples show that more disorders than previously assumed in fact are plasticity disorders.

3.2.5. Developmental disorders

Recent research has indicated that neural plasticity may be involved in some developmental disorders such as autism. It is believed that at least some of the symptoms of some common developmental disorders are caused because the postnatal development (“midcourse correction”) of the nervous system is going awry. There are indications that at least some of the symptoms of autism are caused by the childhood development (“midcourse correction”) discussed above not been carried out correctly.\textsuperscript{32} Common for autism (or rather autism spectrum disorders, because autism is large group of diverse disorders)\textsuperscript{51} are problems with social interactions and many autistic individuals have also have abnormal perception of sensory input and symptoms that indicate abnormal involvement of the emotional brain (mainly the amygdala). It has also been shown that some autistic individuals seem to use their non-classical auditory pathways to a greater extent than what is normal.\textsuperscript{52} While children normally show signs of active non-classical auditory pathways,\textsuperscript{10} the degree of activation decreases with age and it is rare in individuals above the age of 15 in non-autistic children. All this points towards autism being a plasticity disorder.
Other studies\textsuperscript{53)} have shown that the amygdala and other brain structures in autistic children have a higher packing density of cells than normal. This indicates that the postnatal pruning and programmed cell death have been insufficient or incorrectly executed in individuals with autism spectrum disorders.

The reorganization that occurs in early life (“midcourse correction”) affects large regions of the brain including elimination of synapses and axons, and death of entire cells (programmed cell deaths) is common during that period. Little is known about how this reorganization is guided but it may be hypothesized that the program that controls the normal “midcourse correction” that occurs after birth is of genetic and epigenetic in origin and modified by environmental factors (Fig. 6). The programs that control these changes in the brain may be established before birth perhaps by environmental insults to the mother.\textsuperscript{54)} This may explain why attempts to treat these disorders with medications administered during childhood have had little success.

\section*{4. Treatment of plasticity disorders}

Plasticity disorders are characterized by the occurrence of abnormal neural activity in a cascade of neural structures. The structure that constitutes the beginning of this cascade is pathologic and it generates abnormal activity that is transferred to other structures in this chain. The output of structures that receive abnormal input will be abnormal despite they may function normally. For example, deprivation of input can affect the ribonucleic acid (RNA) in the nerve cell that has lost its neural input and that cause change in protein synthesis\textsuperscript{1)} (Fig. 7) causing the output of the cell to become abnormal. The neurons that receive such abnormal activity will produce abnormal activity even when it is functioning normally. The abnormal activity will subsequently reach neurons in the parts of the brain that generate the symptoms and signs of the disorder that in this example was caused by the deprivation of input.
Fig. 7. Hypothetical flow chart of events in a series of structures as a result of deprivation of input. \(^{32}\)

Fig. 8. Hypothetical flowchart of disorders where two factors must be present together in order to cause symptoms of disease.

Fig. 9. Hypothetical flowchart of events that occur in development of type 2 diabetes neuropathy. \(^{32}\)

to the first cell in the chain. Treatment aimed at neural structures that produce abnormal input because they receive abnormal input will not cure the disease although it may ameliorate the symptoms as long as the treatment is applied. This means that treatment of plasticity disorders is subjected to similar obstacles as treatment of many other disorders such as incomplete understanding of pathology and lack of suitable means to intervene with the pathological conditions.

It is hypothesized that a certain program controls pathologic changes in some plasticity disorders such as those caused by faulty midcourse correction discussed above (Fig. 6). The most effective treatment of plasticity disorders would be to aim the therapy at such programs as well as the pathologic signs of other plasticity disorders are controlled by a faulty program (Fig. 8) and therapy aimed at the faulty program would be an effective treatment. However, it is usually difficult to identify the anatomical location of the structures that act as such faulty programs.

As in many other diseases there are often several factors involved in the cause of plasticity disorders. \(^{33}\) In some disorders, the effect of several factors adds and in
other disorders two or more factors must be present at the same time in order that a
disease to become manifest. An example of that is hemifacial spasm where irritation
of the facial nerve root and another (unknown) factor activate neural plasticity caus-
ing the facial motonucleus to become malfunction causing spasm and synkinesis.41)
In such disorders therapy aimed at only one of the (two or more) factors is effec-
tive because symptoms are present only when both factors are present. This makes
this particular form of plasticity disorder similar to such common disorders such as
diabetes type 2 (Fig. 9).

Some structures can operate in two different (stable) modes; one normal and
one pathologic (being bistable). An example is parts of the dorsal horn of the spinal
cord that malfunction causing central neuropathic pain.33),36) Expression of neural
plasticity may create such bistable neural circuits. In order to cure disorders that
are caused by such structures the mode of operation must be switched back to its
normal mode.

Like what is the case for other disorders, prevention is better than treatment. However, lack of understanding of how plasticity disorders are acquired and develop
often makes it difficult to use prevention. Implementing effective preventive means
in general is also hampered by psychological factors such as the impression that
“disorders are something that only affect other people”.

4.1. Neural plasticity and the purposiveness of the brain

The brain is assumed to be purposive.55) Purposiveness (having or serving a
purpose) of the brain has been discussed in connection with the nervous system
and its evolution. The word purposiveness first appeared in a 1943 article.56) These
authors divide active behavior into groups that are purposeless and groups that are
purposeful.

Purposefulness is interpreted as being directed to the attainment of a goal and
purposeless behavior is interpreted as not being directed to a goal. If the goal of
neural plasticity is to change the function of the nervous system, its goal is fulfilled
in most instances and activation of neural plasticity may be regarded as being pur-
poseful (not random) in most instances. Purposiveness is not the same as benefit
to an individual. As we have seen, activation of neural plasticity has different forms
some being of benefit to the individual some not being of benefit.

The changes that make it possible to adapt to changing demands (prostheses
etc.) can be beneficial but also cause diseases thus being harmful (causing plasticity
disorders). Plasticity disorders such as central neuropathic pain and tinnitus cannot
possibly be purposive. The change in the organization of the spinal cord and the
brain causing central neuropathic pain on the other hand does not seem to have
any benefit to the individual and may therefore not be regarded as being purposive.
Causing a disorder may be regarded as being purposeful because it is not random but
it is not beneficial. The re-organization that occurs in childhood is both purposive
and beneficial when performed in the way it is normally executed. This kind of neural
plasticity may be regarded to occur in accordance with Darwinian evolution.57)

Purposiveness also involves intent but natural selection is done without inten-
tional design. According to the theory of Darwin evolution is a design without a
designer. Was the goal of evolution directed (purposive) teleological i.e. was natural selection a purpose-directed design?

While development of beneficial plasticity thus can be explained by Darwinian theories of the survival of the fittest, but it would not explain the development of harmful plasticity (plasticity disorders). Was it a mistake of nature? The question about development of neural plasticity for good or bad may resemble the discussions in theoretical physics regarding whether God played the dice in the development of the universe. Did nature play the dice in biological developments?

The fact that there is harmful neural plasticity (causing plasticity disorders) shows that biologic development is not always beneficial although it may be regarded to be purposive (not random); but the purpose is unknown.

While it seems reasonable to assume that beneficial neural plasticity has developed as a result of natural selection it is difficult to see how natural selection could have favored the development of plasticity disorders. It has been suggested that neural plasticity is a form of adaptation that has developed as a result of natural selection\textsuperscript{57}) and which is beneficial because it provides several forms of “midcourse corrections” that are necessary for normal function and thus beneficial to the individual person and purposive. It could be argued that non-beneficial neural plasticity causing plasticity disorders are caused by maladapative plasticity.

Does nature try to correct its mistakes and will harmful plasticity (plasticity disorders) vanish as development goes forth? Mistakes in evolution may disappear if they cause disadvantages to survival to accomplishment of reproduction.

If the goal of increase in survival by natural selection are to improve reproduction the change must occur before the end of the period of reproduction, which for women is around the age of 40 years and much higher for men. Plasticity disorders such as chronic pain and tinnitus may affect the ability to reproduce but these disorders often occur late in life. As longevity beyond 40 years for women therefore does not affect the ability to reproduce plasticity disorders that occur late in life does not affect the ability to reproduce and thus there is little evolutionary pressure to eliminate such disorders by natural selection.

4.2. Summary

Expression of neural plasticity provides “mid-course corrections” of the organization of the CNS that has been laid down by genetic programs (Darwinian) and which is necessary for normal function and it can make the nervous system adapt to changing demands; it can re-route information to functioning parts of the CNS in case of injury and make information reach other parts of the CNS take over function it normally does not have. Similar kinds of re-organization and changes in function may cause plasticity disorders such as tinnitus and central neuropathic pain where activation of neural plasticity can cause systems to operate in different modes, being “bistable”. The changes in function that occur through activation of neural plasticity may occur through unmasking of dormant synapses, masking of active synapses, by creation of new structures or by elimination of existing connections.
4.3. What is life?

The conference concerned “what is life” and the answer to that very broad question must depend on the person who asks the question (the observer). The task of describing what is life reminds of the Hindu Parable about the six blind men and an elephant by John Godfrey Saxe (1816-1887).

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Neural Plasticity: For Good and Bad