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# Functional neurology: A review

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Narrative: In this review I first identify the conditions that may be assessed using Functional Neurology and then describe the neuron and the many processes associated with neuroplasticity and neural signalling.

Then I offer a comprehensive review of the effects of modalities upon neuroplasticity and neurogenesis, giving mechanisms and signalling pathways relevant to clinical observation. I finish with a discussion on nutrients found to affect cognitive function and propose mechanisms for their effectiveness.

I conclude that the updated concept of functional neurology represents the neuron integrated into its environment and therefore susceptible to modulations of its signalling capacity by a vast array of external factors. These agents of change include both electrical and chemical phenomena triggered by such external interventions as rehabilitation, manual muscle therapy, acupuncture, biofeedback, aromatherapy, yoga, cognitive exercises, eye muscle exercises, mediation, exercise, diet, and botanical nutritional supplements.

Indexing terms: Chiropractic; functional neurology; neuroplasticity; clinical intervention; nutrients.

## Introduction

A discussion of the meaning and scope of functional neurology is perhaps best introduced with a quotation from the individual responsible for the origins of Chiropractic, DD Palmer:

> '*Life is the expression of tone*'. In that sentence is the basic principle of Chiropractic. Tone is the normal degree of nerve tension. Tone is the expression of function by normal elasticity, activity, strength, and excitability of the various organs as observed in a state of heath. Consequently, the cause of disease is any variation of tone, nerves too 'tense' or' static'. (1)

*... The updated concept of functional neurology represents the neuron integrated into its environment and therefore susceptible to modulations of its signalling capacity by a vast array of external factors ...'*

Specifically, functional neurology can be thought of as a master biomarker, in that it utilises an entity that acts as the origin of changes in health that, if left unattended, emerge as symptoms and ultimately as pathologies.

That entity is the nervous system, lending itself to an assortment of noninvasive tests designed to pinpoint the area of neural dysfunction and helping to identify the optimal stimulant to activate that area, ideally before more substantial disorders appear.

Functional neurology is founded on the principle of neuroplasticity, in that nerve connections in the brain may be modified or shaped by a variety of afferents, including sensory, cognitive, emotional, or motor experiences, and thus amenable to rehabilitation. It stands in contrast to previous scientific tenets that brain development is limited to a critical period in early childhood, remaining relatively unchanged thereafter. (2)

Clearly the focus of functional neurology is the conceptualisation of the nervous system as an integrated network which controls the homeostasis of the body through balanced signalling, free from distortions which could lead to a variety of conditions as suggested by Table 1. (3)

**Table 1:** Conditions addressed with functional neurology

**CONDITIONS ADDRESSED WITH FUNCTIONAL NEUROLOGY**

| **Classification of Disorder** | **Examples** |
|---|---|
| Neurological diseases | Parkinson's, Multiple Systems Atrophy (MSA), Alzheimer's, Huntington's, dementia, Progressive Supranuclear Palsy (PSP), Amylotrophic lateral sclerosis (ALS) |
| Demyelinating diseases | Multiple sclerosis (MS), transverse myelitis, $B_{12}$ deficiency |
| Movement disorders | Dystonia, torticollis, blepharospasm, tremor, myoclonus, tics, chorea, restless legs syndrome, dyspraxia |
| Ear/equilibrium problems | Vertigo, dizziness, motion sickness, labyrinthitis, vestibular neuronitis, acoustic neuroma, mal de debarquement, Meniere's disease, ataxia, benign paroxysmal positional vertigo (BPPV), fear of falling, tinnitus |
| Headaches and pain syndrome | Migraine, cluster headache, tension headache, chronic pain, complex regional pain syndrome (CRPS), Reflex sympathetic dystrophy (RSD), causalgia, fibromyalgia |
| Traumatic injuries | Concussion, traumatic brain injury (TBI), whiplash |
| Seizure disorders | Epilepsy |
| Cerebrovascular conditions | Stroke, transient ischemic attack (TIA) |
| Nerve, nerve root and plexus Disorders | Trigeminal neuralgia, Bell's palsy, brachial plexus lesion, disc herniation, canal stenosis, intermittent claudication, carpal tunnel syndrome, sciatica, meralgia parasthetica, cheiralgia paresthetica, morton's metatarsalgia, tarsal tunnel syndrome, Intercostal neuropathy, thoracic outlet syndrome (TOS), polyneuropathy |
| Neurodevelopmental problems | Autism, Attention Deficit Disorder (ADD/ADHD), Asperger's, Tourette syndrome (TS), Obsessive compulsive disorder (OCD), pervasive developmental disorder (PDD), Dyslexia, processing disorders, dyspraxia, learning disability, language developmental Delay, global developmental delay, Down syndrome, cerebral palsy (CP) |

The positive aspect of functional neurology is that a reorganisation of nerve cells is possible to restore or bypass the connections that have become disrupted or damaged, a perfect example being exercises to recover from stroke. The negative aspect, however, is that if a neuronal pathway is not fired, synaptic connections may become inactive with the loss or inactivation of neurotransmitters and receptors, as exemplified by the abundance of mental exercises designed to forestall cognitive decline in the elderly. (4, 5)

It can be concluded from the preceding discussion that functional neurology is an approach that is multidisciplinary, open to conceptual and therapeutic contributions from any of an extensive variety of healthcare professions, including medical doctors, doctors of osteopathy, Chiropractors, doctors of naturopathy, physical therapists, occupational therapists, doctors of optometry, doctors of oriental medicine and acupuncture, dentists, and nurse practitioners, as well as toxicologists and neuroscientists.

> The focus of functional neurology is upon strategies to promote brain function with attention to brain exercises, diet, nutrition, lifestyle, and environmental factors.

## The neuron

An understanding of functional neurology should begin with the neuron. (6) Here it is a matter of assessing the likelihood that the neuron will produce an action potential, depending upon its state of polarisation. This, in turn, depends upon the sum total of the excitatory and inhibitory stimuli that it encounters at any given moment. If the neuron is in a depolarised state, the cell has become more positive internally, minimising the potential difference across the membrane and thereby moving the neuron toward its firing threshold.

This may be accomplished by the movement of positive sodium ions into the cell. Conversely, hyperpolarisation occurs when the cell interior has become more negative, increasing the potential difference across the membrane and causing the neuron to back away from its firing threshold. This state may be achieved by the efflux of positive potassium ions from the cell's interior or by the entrance of negative chloride ions into the neuron.

Calcium ions may also be involved in modulating membrane permeability and thus the firing threshold. Ion movements across the membrane are achieved through what are known as voltage gated channels. The depolarisation and hyperpolarisation cycle involving sodium and potassium ions is illustration in Figure 1. (7)

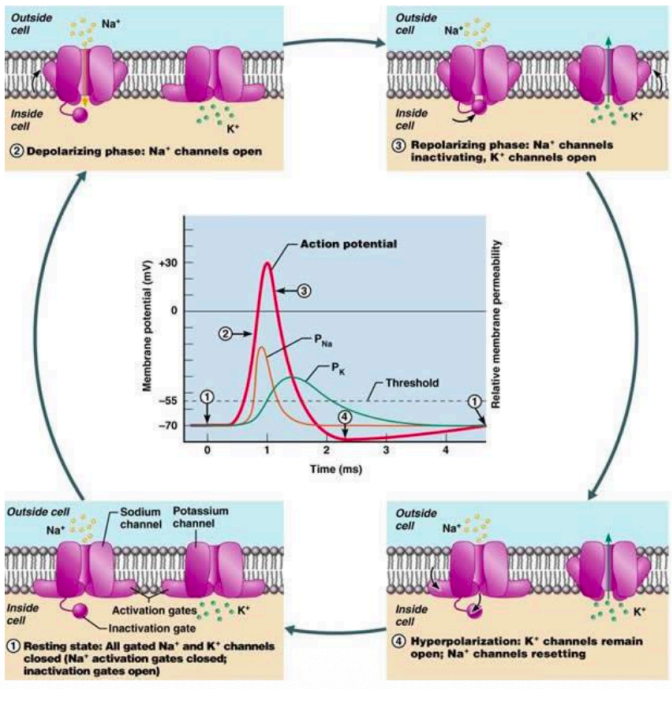



**Figure 1:** Firing and quiescence of the neuron: Mechanism of action via polarisation and depolarisation

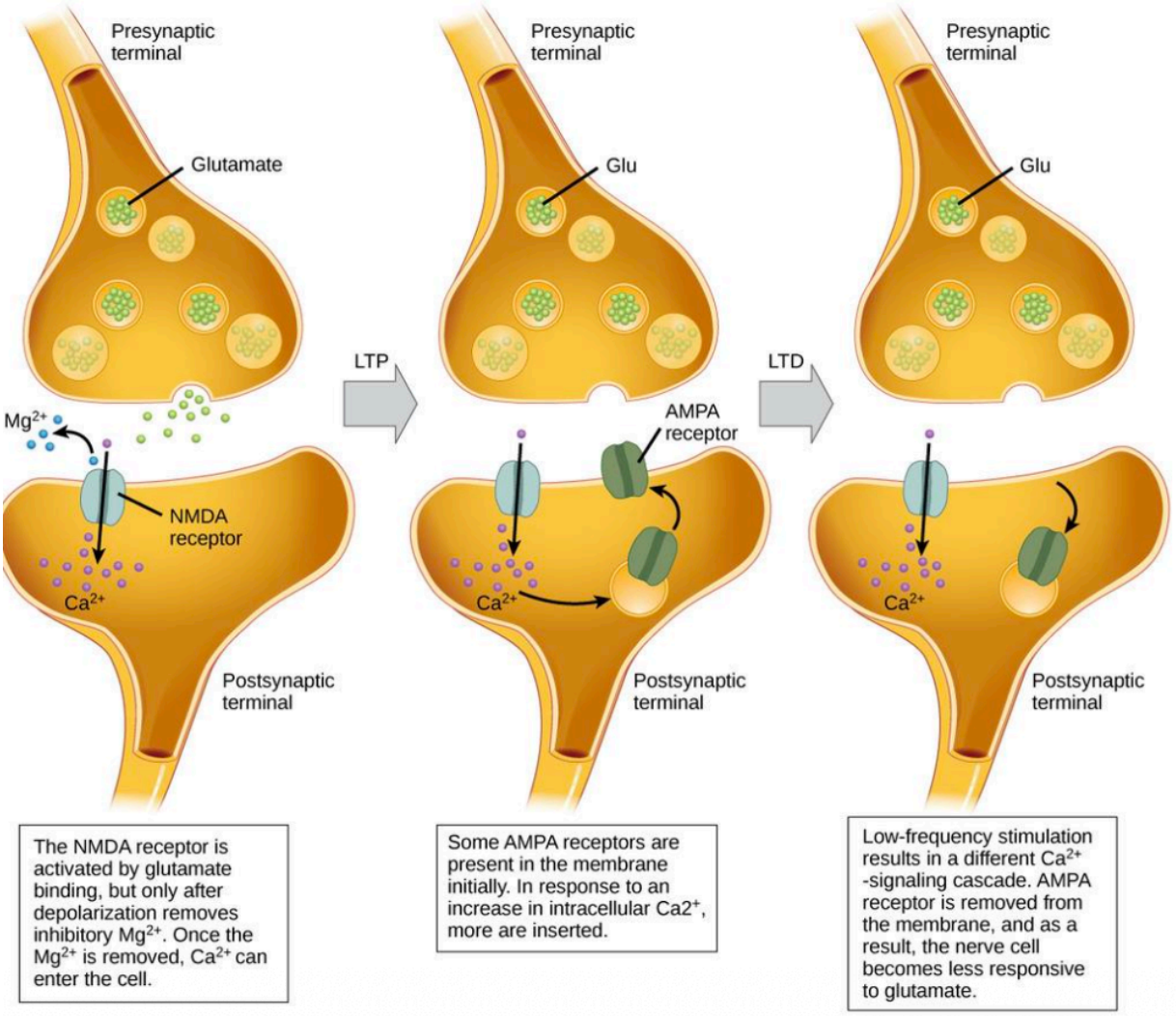
## Neuroplasticity

The reorganisation of nerve cells is the core concept of functional neurology; i.e., changes in the physiological function of the neuro-axis in response to changes in the immediate or external surroundings, was first identified anatomically in 1964 when the histology of the rat cerebral cortex was found to respond to environmental changes. (8) But indications of the brain's ability to reorganise in response to the environment were reported over a century ago in the writings of Shepherd Ivory Franz, who first reported that monkeys that were subjected to mechanical stimulation of the peripheral nerves and muscles recovered from an induced paralysed condition of the arm to normal movement. (9) That same year, Franz and two coauthors reported in 5 subjects with paralysis of 5-20 years' duration that voluntary motor control was restored with a rehabilitation program including massage, and shaking of the affected limb. (10)

Franz speculated that '*it is apparent that some possibility of functional adaptation exists in the brain for certain types of movements so that when a certain 'centre' and its connected muscles cannot be utilised, other 'centres' and their connecting muscles may be brought into play to bring about the desired result*'. (11) It was just 30 years ago, however, that the World Health Organisation acknowledged that neuroplasticity could play a role in the repair of the central nervous system and thus might be a factor in effective healthcare interventions. (12) Not long afterward, these therapeutic interventions were soon deemed to be effective in counteracting lesions of the central nervous system regardless of whether they were applied acutely, sub-acutely, or late after injury. (13)

More recently, Carrick demonstrated in a double blind randomised controlled trial that eye movement training produced changes in quantitative electroencephalogram patterns and in the NIH Stroke Scale in patients suffering from acute middle cerebral artery ischemic stroke, compared to a control group treated only with aspirin. The conclusion was that the eye movement training could induce altered brain activation to accompany the functionality of saccades. (14). Examples of plasticity at the synaptic level can be illustrated in Figure 2. (15)

Figure 2: Long-term potentiation and depression. Calcium entry through postsynaptic n-methyl-D-aspartate (NMDA) receptors can initiate two different forms of synaptic plasticity: (i) long-term potentiation (LTP) and (ii) long-term depression (LTD). LTP arises when a single synapse is repeatedly stimulated. The stimulation causes a calcium- and CaMKII-dependent cellular cascade, which results in the insertion of more α-amino-3- hydroxyl-5-methyl-4-isoxazole propionate (AMPA) receptors into the postsynaptic membrane. The next time glutamate is released from the presynaptic cell, it will bind to both NMDA and the newly-inserted AMPA receptors, thus depolarising the membrane more efficiently. LTD occurs when a few glutamate molecules bind to NMDA receptors at a synapse (due to a low firing rate of the presynaptic neuron). The calcium that does flow through NMDA receptors initiates a different calcineurin and protein phosphatase 1-dependent cascade, which results in the endocytosis of AMPA receptors. This makes the postsynaptic neuron less responsive to glutamate released from the presynaptic neuron.




Neuroplasticity was shown to be not limited to neural injury and recovery. It includes dendritic remodelling, synapse turnover, long-term potentiation, and neurogenesis. In terms of human welfare, it encompasses brain development, the learning of skills, the formation and loss of memory, and self-repair from neural injuries. (16)

For example, Carrick reported in a trial involving healthy volunteers that manipulation of the second cervical motion segment produced what was evidently an enlargement in the circumferential measurement of the blind-spot map associated with decreased cortical activity in only one cortical hemisphere. In other words, this particular intervention may have been associated with a change in brain function. (17)

Even more intriguing was the observation that changes in hippocampal structure could be found in London taxi drivers as they became familiar with the city's layout, shown by a redistribution of grey matter compared to controls. (18, 19)

Because models in structural pathology fail to adequately account for several clinical and experimental findings in individuals with chronic musculoskeletal disorders, and because treatments guided by these models fail to effectively treat many chronic disorders, alternative paradigms are being sought.

The model of neuroplasticity, addressing changes in the central nervous system, has been proposed to be the missing link to our understanding of chronic musculoskeletal disorders. (20)

## Neurogenesis

Neurogenesis refers to the birth and proliferation of new neurons in the brain, occurring then stem cells located in the dentate gyrus, the hippocampus, and possibly the prefrontal cortex split into a stem cell and a cell that becomes a neuron with axon and dendrites, the latter capable of migrating into an area of the brain where it is needed. For centuries the belief was maintained that the ability of the brain and spinal cord to regenerate was limited to embryonic development, and that damage to these organs thereafter tended to be permanent. But this changed in 1962 when Joseph Altman found that several areas of the rat brain were capable of incorporating radioactive thymidine into the DNA, (21) including the olfactory bulb and dentate gyrus. (22)

Yet interest in brain regeneration languished until 1993, when rat brain stem cells were found to proliferate in vitro by the addition of growth factors, growing into cell aggregates called 'neurospheres' which differentiated into neurons and glia. (23) Neuroblasts generated in the subventricular zone of the dentate gyrus were shown to migrate to the adult olfactory bulb and differentiate into neurons, (24) creating the impression that grafted neurons had the potential to migrate within the brain. Neurons have also been suggested under certain conditions to migrate to regions other than the olfactory bulb and dentate gyrus. (25)

It does appear that adult neurogenesis offers the opportunity to learn how neurons integrate into mature brain circuits, (26) while at the same time it appears that altering the environment in which neuronal stem cells may differentiate will not alter the type of neurons that they produce. (27, 28) The fact remains, however, that the human hippocampus retains its ability to generate neurons throughout life. (29)

## Neurotransmitters and receptors

The actual generation of action potentials occurs in a region of the axon known as the hillock area, (30) sending the potential through the length of the axon to its terminal region. Here the potential triggers the release of chemical neurotransmitters into the synapse, a gap which separates the cell from its nearest neighbouring neuron. It is the neurotransmitter which enables the action potential to reach the next neuron in a chain reaction, binding at the neighbouring cell's surface to specialised receptors which reactivate the action potential through that neuron, as shown in Figure 3. (31)

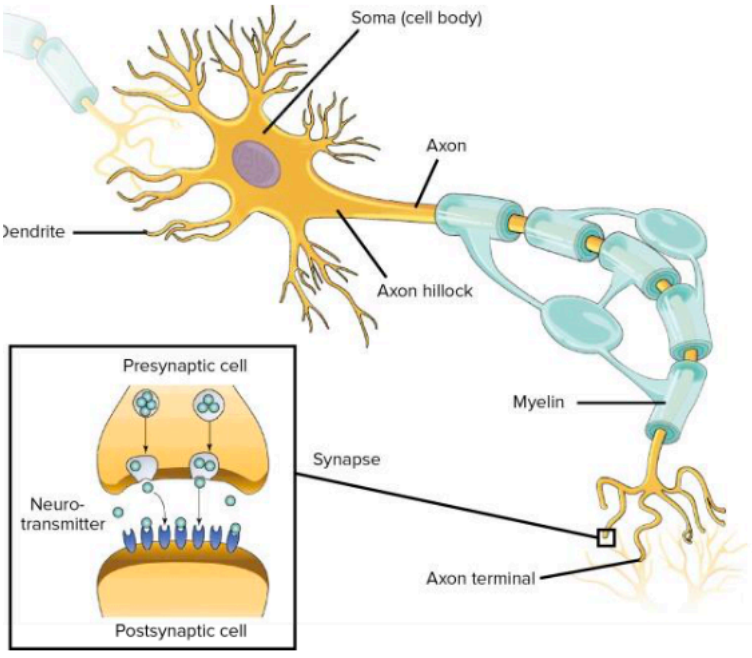



**Figure 3:** Structure of neuron and transmission of action potential by neurotransmitters.

The most prominent neurotransmitters involved in neural regulation at the molecular level in functional neurology are, as follows:

### *Acetylcholine*

A closer examination of the role of the neurotransmitters at the synapse provides a biochemical clue as to how the regulation of nerve signalling by molecular intermediates may occur. (32) Using acetylcholine as a typical neurotransmitter, Figure 3 illustrates how:

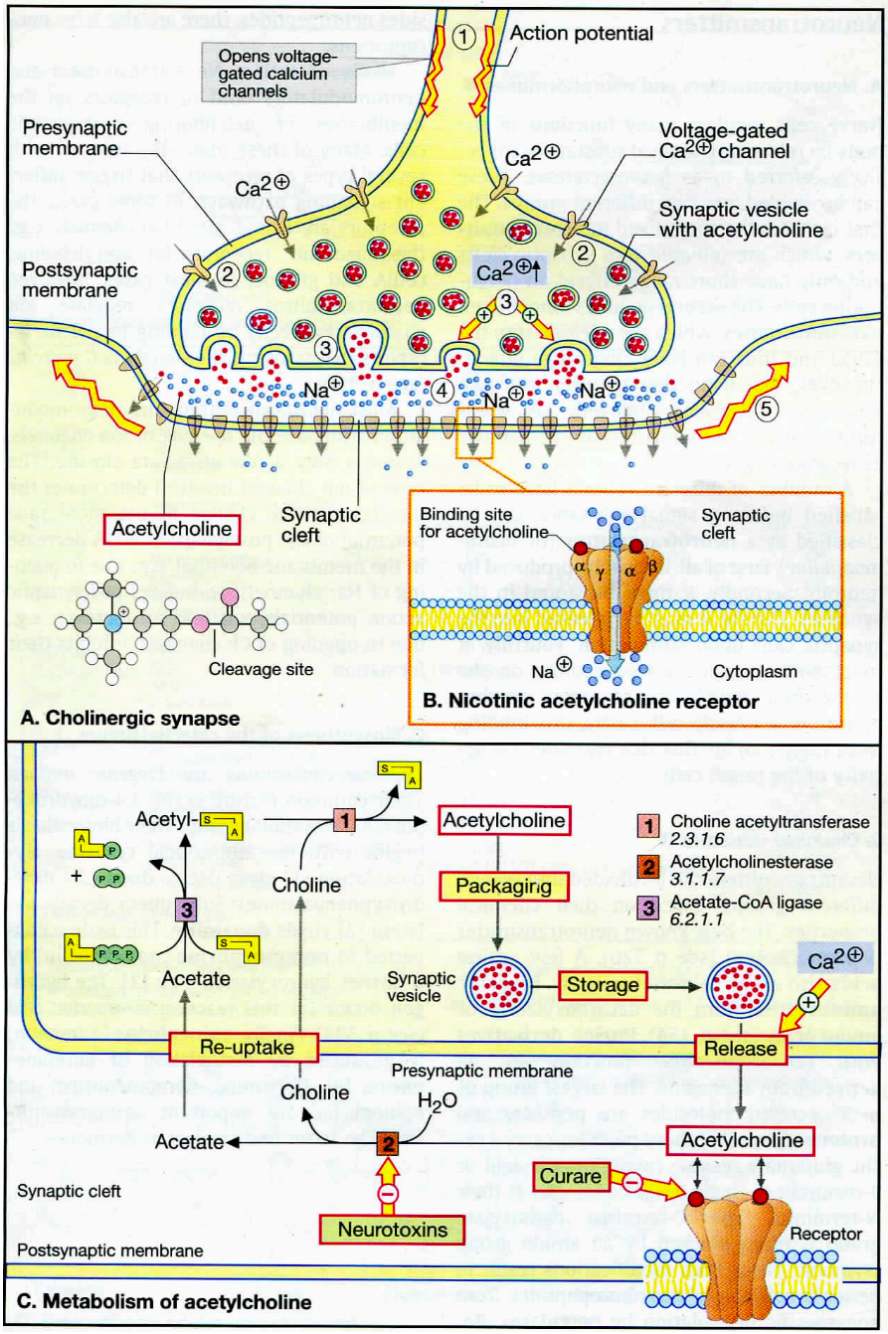
1. The action potential traveling down the length of the axon causes voltage-gated calcium channels to open, leading to the influx of $Ca^{+2}$ ions from the extracellular space.
2. By means of an exocytotic process, $Ca^{+2}$ releases a neurotransmitter (acetylcholine) from vesicle entrapment, allowing acetylcholine to enter the synaptic (cholinergic) cleft.
3. Acetylcholine binds to a specific nicotinic acetylcholine receptor on the neighbouring neuron, raising the resting potential of the postsynaptic nerve or muscle cell, opening a channel for sodium to enter the cell and trigger an action potential as discussed above.
4. Numerous poisons may either block acetylcholine from binding to its receptor (curare) or prevent its being recycled into its neuron of origin as acetate and choline (neurotoxins).

This chain of events leads one to suspect that neurotransmitters may be the locus of the regulation of signalling between neurons. To qualify as a neurotransmitter, the chemical must satisfy five criteria: (32)

1. It must be produced by neurons
2. It must be stored in the synapses
3. It must be released into the synaptic cleft upon stimulation
4. It must bind specifically to receptors on the postsynaptic membrane of either another neuron or muscle cell, and
5. The binding must trigger an ion influx that governs the activity of the target cell.

What we illustrate in Figure 4 represents the basic essentials of but one of the abundant neurotransmitter-initiated pathways of nerve transmission.

**Figure 4:** Acetylcholine-mediated mechanism of neural transmission. (A) Cholinergic response; (B) Nicotinic acetylcholine receptor; (C) Metabolism of acetylcholine.




While acetylcholine is the best known neurotransmitter, amino acids, biogenic amines, purine derivatives from adenosine, peptides and proteins are also members of this neuromodulator. Other neurotransmitter-receptor complexes therefore need to be noted as well. The nicotinic receptor as a ligand-gated ion channel functions for gamma-amino butyric acid and glycine as well as for acetylcholine. Most neurotransmitter receptors control ion channels indirectly by binding to 7-helix receptors which transmit the signal via G proteins. The latter, consisting of three dissimilar subunits, allow an exchange of bound GDP for GTP and ultimately generates what is known as a second messenger. Second messengers include cyclic AMP (cAMP), cyclic GMP (cGMP), diacylglycerol, inositol triphosphate, calcium, and arachidonate. Among their other functions is the ability of second messengers to allow signal amplification within the cell. The end result of receptor stimulation at the synapse is to provoke DNA transcription of appropriate genes to produce proteins and neurotransmitters.

Other products to follow are cytoskeletons, membrane receptors and channels, and enzymes.

### *Gamma amino butyric acid*

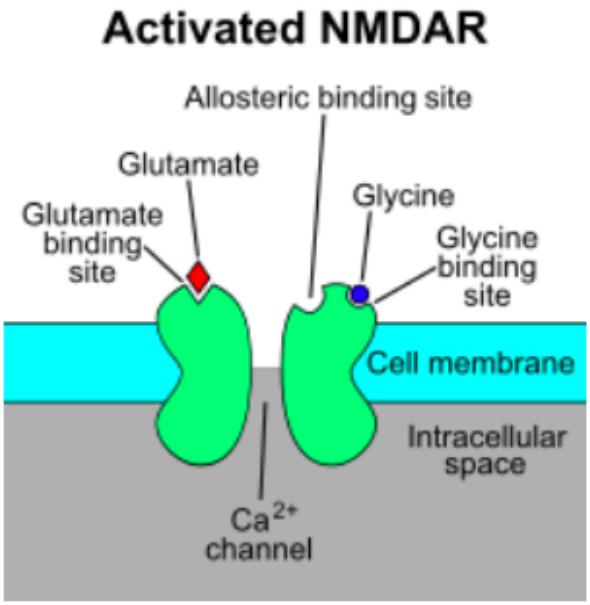
A more representative and far more complex neurotransmitter in functional neurology is gamma-amino butyric acid (GABA), which acts as the primary inhibitory neurotransmitter in the mammalian central nervous system, playing a key role in modulating neuronal activity. No less than three classes of GABA receptors exist:

1. $GABA_A$: Electrophysiogical studies have indicated that the $GABA_A$-receptor complex rapidly mediates an increase in membrane conductance that is often accompanied by membrane hyperpolarisation. The result of this is an increase of the firing threshold and thus the reduction of spontaneous initiation, leading to overall neuronal inhibition with the membrane potential stabilised to near the resting level. With a damping of postsynaptic depolarisation achieved, there is the reduced likelihood of brain function from overreacting from excessive initiation of action potentials. The GABAergic synapse has been shown to have a far more complex structure than the acetylcholine receptor shown in Figure 4, although the basic mode of action in chemical transmission of signals across the synaptic cleft is essentially the same. (33)
2. $GABA_B$: These are guanine nucleotide-binding (G) protein coupled receptors, the function of which is to modulate $Ca^{+2}$ and $K^+$ channels, capable of eliciting both presynaptic and postsynaptic inhibition. They have a broad range of expression in the nervous system:
   - modulating synaptic excitability and placidity in the cerebral cortex
   - generating rhythmic activity in cortical and thalamic circuits
   - relaying primary afferent input to the spinal cord and brainstem, and affecting the activity of dopaminergic and other monoaminergic neurons. (34) Unlike the fast synaptic acting $GABA_A$ receptors, $GABA_B$ receptors exert a slow inhibitory potential. (35)
3. $GABA_C$: Like their $GABA_A$ counterparts, $GABA_C$ receptors are linked to chloride channels but are slow rather than fast-acting and also are insensitive to the benzodiazepines and anaesthetics that affect $GABA_A$ receptors. (36, 37) Dopamine has been reported to modulate this receptor activity in both catfish cone-driven horizontal cells (38) and tiger salamander bipolar cell terminals. (39)

### *N methyl D-aspartate*

The leading molecular species for controlling synaptic plasticity and memory function has been identified as the N-methyl-D-aspartate (NMDA) receptor. (40) It is so named due to the selective binding of the agonist molecule NMDA to it and not to other glutamate receptors. It is an ion channel protein located in neurons, activated when both glutamate and glycine (or D-serine) bind to it. This allows positively charged ions, such as calcium ($Ca^{+2}$), to flow through the cell membrane. (41, 42) (Figure 5) The increase of $Ca^{+2}$ within the cell allows it to function as a second messenger in a variety of signalling pathways. However, extracellular magnesium ($Mg^{+2}$) (43) or zinc ($Zn^{+2}$) can bind to specific sites and prevent $Ca^{+2}$ binding and activation. It is only with depolarisation of the cell that $Mg^{+2}$ or $Zn^{+2}$ can be dislodged from the pore, permitting a voltage-dependent flow of $Ca^{+2}$ or sodium ($Na^+$) ions into the cell and potassium ($K^+$) ions out of the cell. (44, 45)

**Figure 5:** Activation of the NMDA receptor (NMDAR) by glutamate and glycine, opening channel for $Ca^{+2}$




NMDA receptors are associated with synaptic plasticity, shown perhaps most directly by the demonstration that extra-synaptic NMDA receptors inhibit long term potentiation while producing long term depression, (46) while the inhibition is prevented by introducing an NMDA antagonist. (47) One of six subunits of the protein identified as NR2B has been pinpointed as a locus of plasticity since the ratio of NR2B to NR2A decreases with age in diverse animal species (including humans) starting on or before sexual maturity. In other words, the relative abundance of NR2B in the juvenile brain appears to confer upon it a greater plasticity than the adult brain.

Interestingly, NMDARs have been identified outside as well as within the synapse. In research conducted over the past decade, the NMDARs outside of the synapse have been found to play a major role in excitotoxicity and cell death, while physiological activation of the NMDARs inside of the synapse can contribute to cell survival. This has led the authors of a review to suggest that preventing excessive activation of the extrasynaptic NMDARs could provide therapeutic benefit in such cases as Alzheimer disease or Huntington disease. (47)

### *Dopamine*

Dopamine belongs in both the catecholamine and phenethylamine families and plays a dual role, serving as

1. the primary neurotransmitter in the brain, and
2. a local chemical messenger outside of the nervous system. Able to cross the blood-brain barrier, dopamine is confined primarily to: (48)

    i. The nigro-striatal tract, consisting of dopaminergic neurons originating in the substantia nigra projecting into the striatum. This tract is believed to be involved in the control of motor movement,

ii. The mesolimbic tract, consisting of dopaminergic neurons projecting from the ventral segmental area into the nucleus accumbens, frontal cortex, and hippocampus. This particular region is believed to be involved in motivation, reward, and learning.

These regions are outlined in Figure 6. (49)

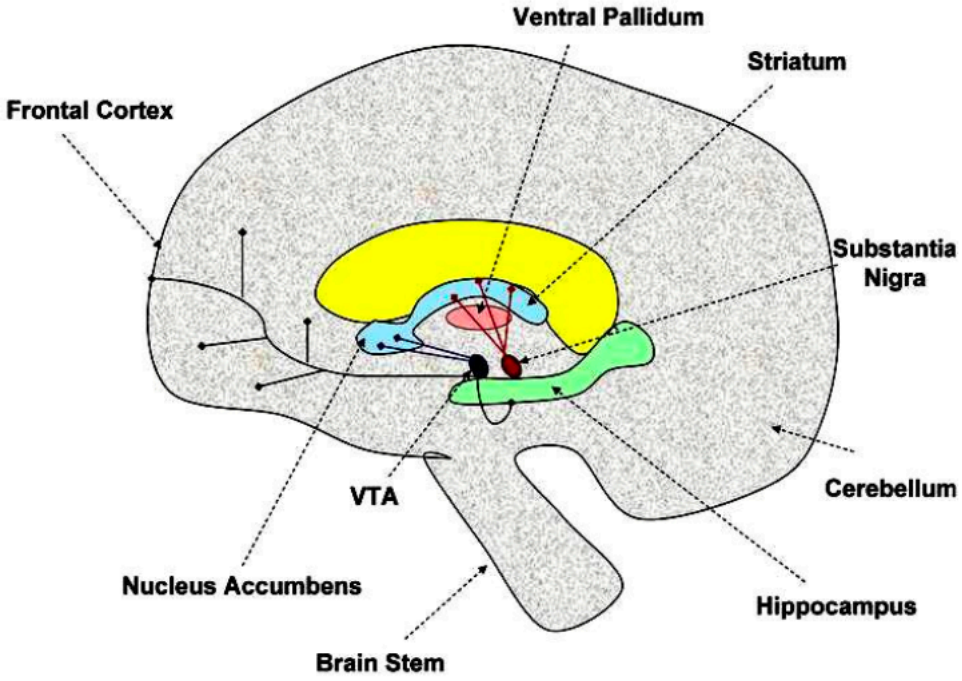



Figure 6: Dopaminergic tracts in the brain. RED = nigro-striatal tract; PURPLE = mesolimbic tract; VTA =ventral tegmental area; DASHED ARROWS = specific brain regions; SOLID ARROWS IN CENTER =dopaminergic neuronal tracts

As with most biologically active substances, dopamine exerts its effects by means of specific binding to and activating receptors. Two evolutionary and genetically different subtypes of receptors exist within the dopaminergic system (D1-like and D2-like) with a total of five distinct receptor classes in all. (50) The two receptor classes, when stimulated by a common agonist, produced an increase of intracellular calcium via a signalling pathway that was not activated by either receptor alone or when only one of the co-expressed receptors was activated by a selective agonist. (51) The consequences of the calcium stimulation produce changes in gene expression, protein production, enzyme levels, the cells' firing rate, and the neuron's sensitivity to dopamine itself. It begins as the cell uses calcium to build and strengthen synaptic connections to other neurons, releasing the calcium from vesicles stored within the neuron as shown in Figure 4.

The physiological effects of dopamine expressed downstream include the following:

1. Gene expression: Immediate early genes that are activated in dopaminergic neurons following stimulation include those of the fos family, (52, 53, 54) fos being a transcription factor that is upregulated in the brain following stimulation from drugs or other rewarding stimuli such as sexual behaviour or exercise. (54)

2. Expression of numerous neuropeptides: Dopamine signalling has been shown to have direct effects upon the expressions of:
   - Substance P (55)
   - Dynorphin (56)
   - Enkephalin (57)
   - Orexin (58)
3. Regulation of motor movement control: Purposeful exercise and/or movement that expends a significant amount of energy is regulated by the dopamine system. (59, 60) Derangements of the dopamine system play a central role in the development of Parkinson's disease (61) and Attention Deficit Hyperactivity Disorder. (62)
4. Mediation of behavioural responses to rewarding stimuli: It is generally accepted that the dopamine system is involved in reward and reinforcing mechanisms, as shown by the results of psychostimulant administration. (59, 63) It functions both as the centre of motivation or wanting as well as being directly affected by the physical activity involved in the pursuit of those entities desired. (64, 65, 66)

Figure 7 presents an overview of the dopamine pathways in the brain and their downstream effects. (67)

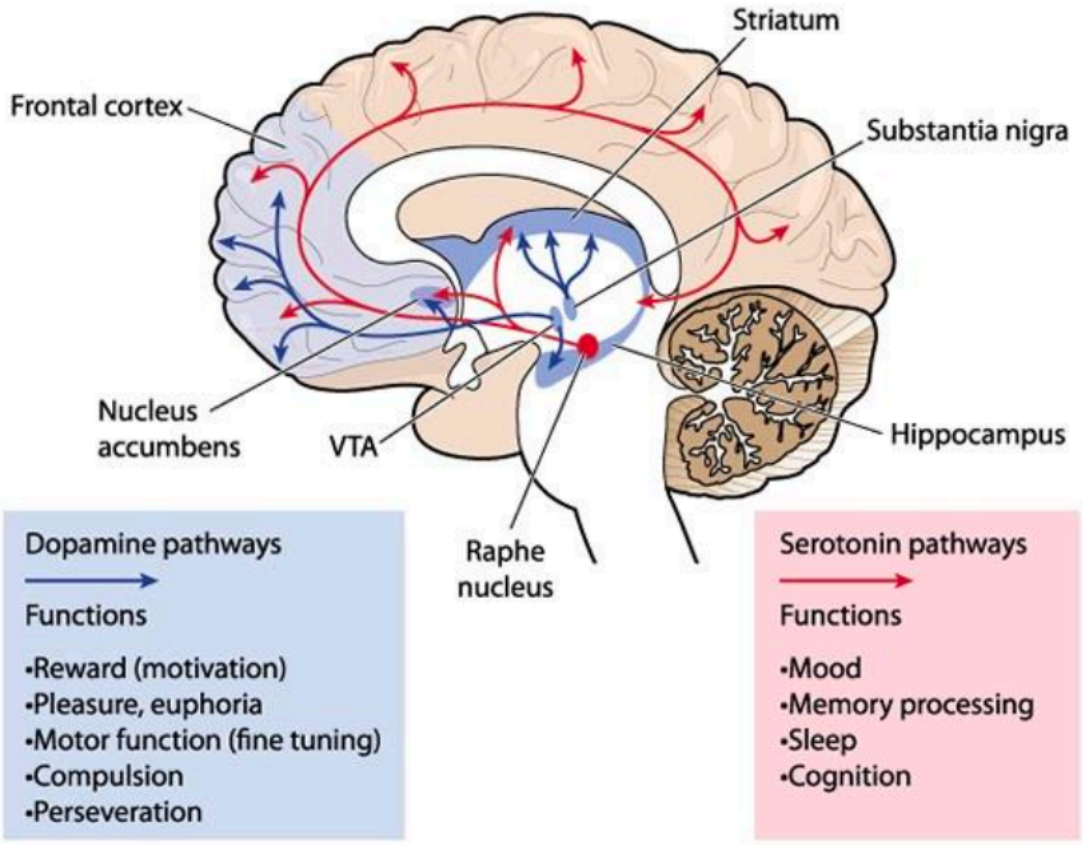



**Figure 7:** Dopamine and serotonin pathways in the brain and behavioural functions

Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter with multiple biological effects, synthesised from tryptophan. It is bound to a transporter protein known as 5-HTT located in the presynaptic cell membrane and responsible for the re-uptake of serotonin into its cell of origin after it has been released into the synaptic cleft to signal the adjacent neuron. The length of time that the chemical signal remains in the synapse is determined by the number and activity of the 5-HTT proteins. (68) Figure 8 illustrates these steps. (69)

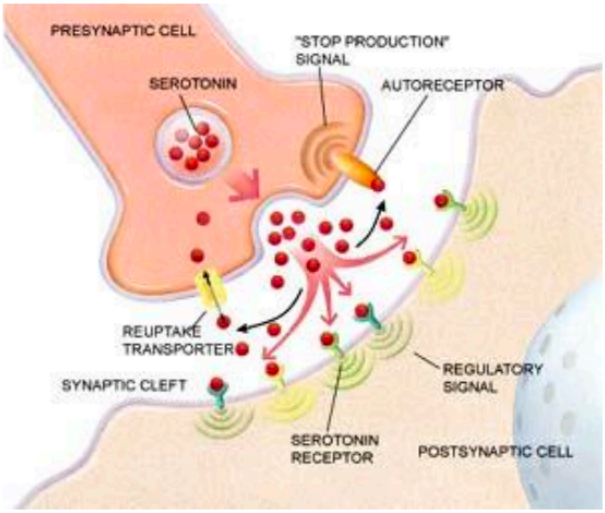



**Figure 8:** Function of serotonin and serotonin transporter. Serotonin is released from the presynaptic cell and bound to receptors on the postsynaptic cell. Transporter protein returns serotonin to the presynaptic cell, terminating serotonin action but allowing serotonin to be recycled if it is not metabolised.

Many of serotonin's function can be described at the molecular level as follows:

1. Regulator of mood: The popular conception of serotonin is that it enhances feelings of content and happiness. (70) Indeed, serotonin has a pervasive influence upon brain activity, being released from axons originating largely in the raphe nucleus of the brainstem but spreading into almost all brain areas. This diffuse mode of action differs from the rapid activity at the synapses, as shown in Figure 7, in which extracellular levels of serotonin will be highly sensitive to the rate at which it is removed.
2. Modulation of nitric oxide synthase: Numerous lines of evidence suggest that the production of nitric oxide is regulated by the 5-HTT transporter. (71)
3. Activation of hypothalamic-pituitary axis: Stimulation of the HPA axis in response to serotonin has been suggested in a mouse model, seen with the abundant expression of serotonin 2C receptors I the paraventricular nucleus of the hypothalamus linked to the activity of corticotropin-releasing hormone. (72)
4. Regulation of glucose balance: Serotonin 2C receptors have been shown to improve glucose tolerance and reduce plasma insulin in mouse models of obesity and type 2 diabetes. Downstream activation of melanocortin-4 receptors was identified as the mechanism involved, a matter of possible clinical significance since pro-

opionmelanocortin neurons, found in the hypothalamus, are known to play a key role in suppressing appetite and inducing weight loss. (73)

5. Regulation of bone metabolism: Gut-derived serotonin regulates osteoblast proliferation and bone formation, while brain-derived serotonin regulates bone mass through the sympathetic nervous system. (74)

In addition to those factors regulating neurotransmitter activity are those pertaining to the neuron itself. These would include an adequate supply of nutrients, cofactors, and essential compounds as well as assuring the sufficient exchange of oxygen and carbon dioxide. Lack of these compromises the production of protein as the result of what is known as transneural degeneration. Resulting from this is the neuron's initial increase irritability, the elevation of its sensitivity to stimulation. But this hyperactivity can last for only a relatively short period of time in the face of deficient nutrients, so that the loss and degradation of microfilaments and microtubules as well as of membrane integrity allows calcium ions to enter unimpeded, resulting in cell death.

These detrimental effects may then be transmitted downstream in a process known as diaschisis. (6)

It is important to recognise that, while such receptors as those that respond to gravity or which maintain pacemaker depolarisation are constant in nature, most receptor systems are not and are thus periodically activated with surges of activity. The latter would include the cortical cells of vision or of memory which experience interruptions with disuse, such as in sleep or neglect. Yet these neurons are sustained to subthreshold activation by complex multineuron systems. (5)

## Neural networks: Excitation and inhibition

Neurons are able to receive signals from up to 10,000 presynaptic neurons and likewise can deliver contacts to a like number of postsynaptic neurons. Understandably, this capability gives rise to enormously complex neuronal circuits. Some of the more basic circuit configurations are shown in Figure 9. (75)

Hyperexcited states of neurons, known as 'wind-up', suggests an inappropriate degree of output per unit input. Neuronal damage can result from: (30)

1. Overactivation of the NMDA receptors, resulting in cytotoxicity due to increased intracellular $Ca^{+2}$ concentrations.
2. Formation of free radicals from anaerobic energy production pathways, leading to damage to membranes and membrane receptor structures, or to mutations in DNA.
3. Transneural degeneration, occurring when intracellular protein and energy stores fall below the level needed to support the increased demands of hyperactivity.

A translation of these networks onto a clinical platform is exemplified by the schematic in Figure 10, in which both the direct and indirect pathways of motor circuits of the basal ganglia are shown in both the normal and Parkinsonian states. (76, 77)

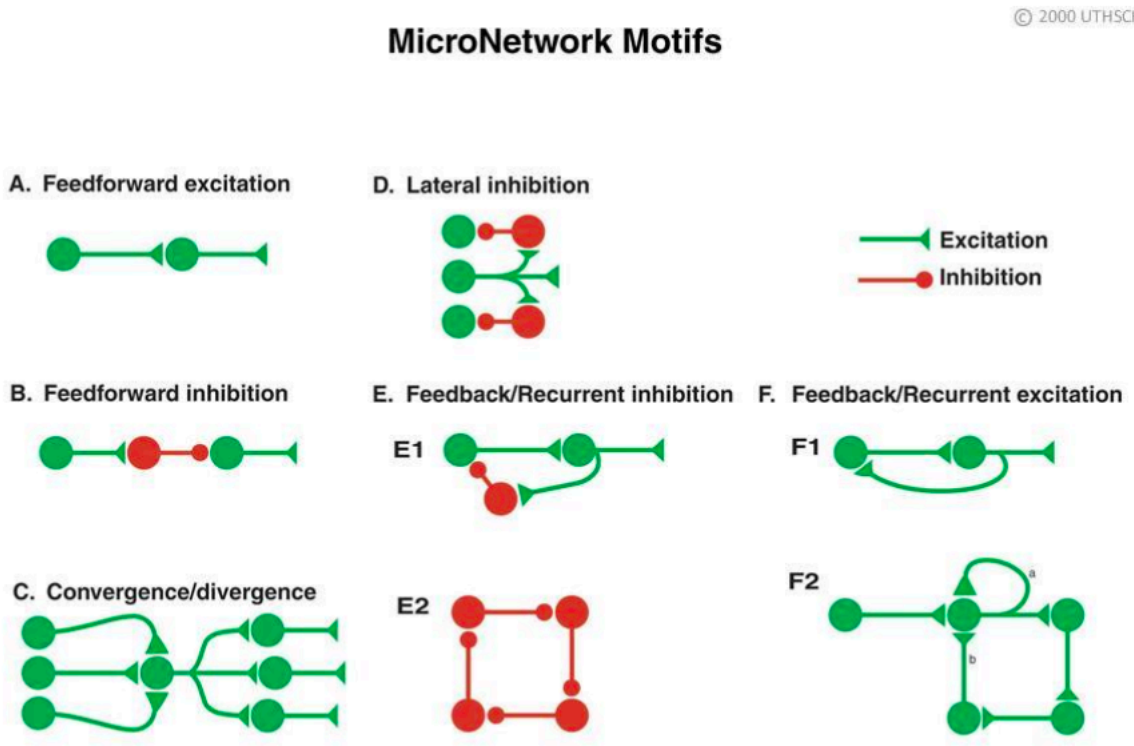



**Figure 9:** Basic neuronal networks involved in inhibition and excitation of signalling.
**A) Feedforward excitation:** One neuron relays information to its neighbour, moving the membrane potential closer to the threshold of firing and generating an action potential.
**(B) Feedforward inhibition:** A presynaptic cell excites an inhibitory interneuron, which then inhibits it next succeeding cell. Its role is to limit or shut down excitation in a downstream neuron by moving its membrane potential away from the threshold of firing.
**(C) Convergence/divergence:** A postsynaptic cell receives convergent input from multiple presynaptic cells, while any individual neuron can make divergent connections to multiple postsynaptic cells.
**(D) Lateral inhibition:** A presynaptic cell excites inhibitory neurons, which in turn inhibit neighbouring cells in the network.
**(E) Feedback/recurrent inhibition:**
**(E1):** A presynaptic cell connects to a postsynaptic cell, the latter connected to an interneuron which in turn inhibits the presynaptic cell.
**(E2):** Each neuron in the closed chain inhibits the neuron to which it is connected. This apparently quiescent pattern can lead to complex spike activity.
**(F) Feedback/recurrent excitation:**
**(F1)**: A presynaptic neuron excites a postsynaptic neuron, which in turn excites the presynaptic neuron, the activation thus being perpetuated.
**(F2):** A presynaptic neuron excites a postsynaptic neuron, which in turn excites itself either directly or indirectly via other postsynaptic neurons.

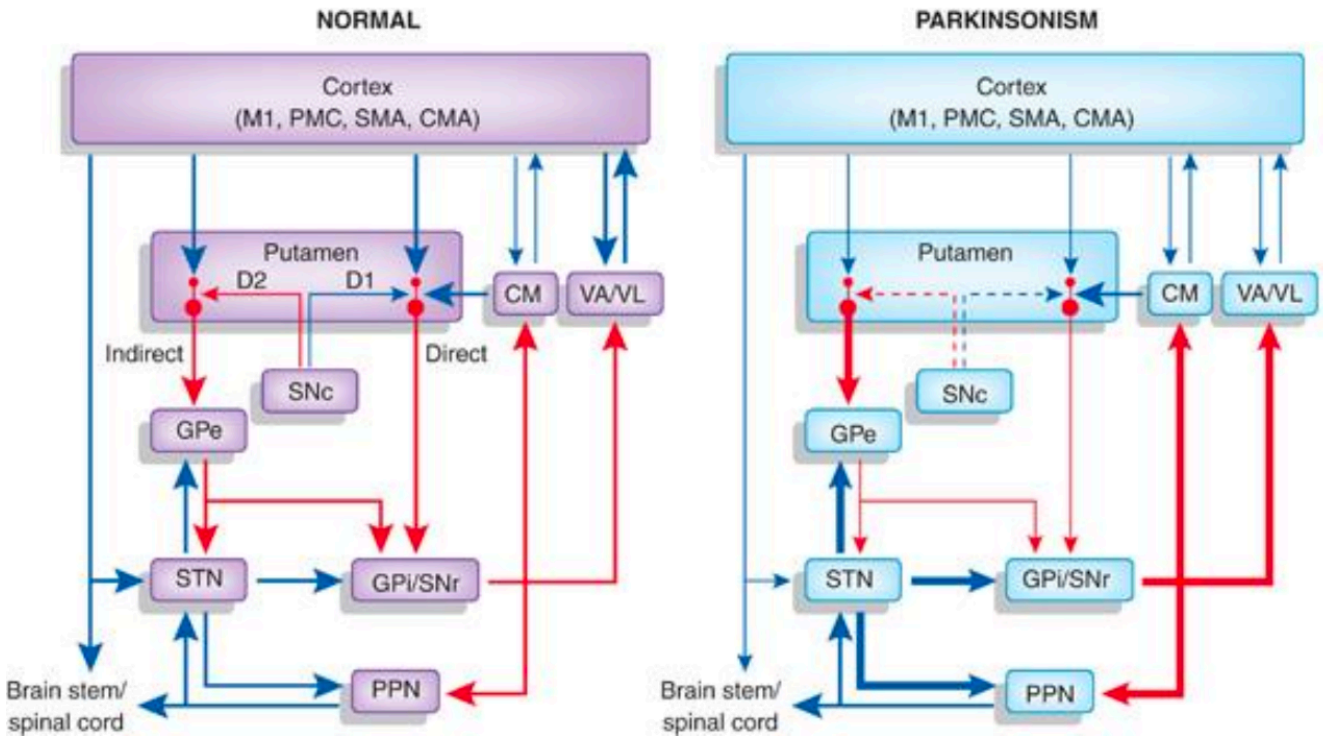



**Figure 10:** Direct and indirect pathways of the basal ganglia motor circuits in normal and Parkinsonian states.
Red arrows: Inhibitory projections; Blue arrows: Excitatory projections; Changes in arrow thickness represent proposed increases (thicker) or decreases (thinner) in the firing rate activity of specific connections.
Dashed arrows labelling dopaminergic projections D1 and D2 from the SNc to the putamen in Parkinsonism indicate the partial lesion of that system.

Many connections have been omitted from this diagram.

Key:

**CM:** centromedian nucleus
**CMA:** cingulate motor area
**GPe:** globus pallidus, external segment
**GPi:** globus pallidus, internal segment
**M1:** primary motor cortex; PMC: pre-motor cortex
**PPN:** pedunculopontine nucleus
**SMA:** supplementary motor area
**SNc:** substantia nigra pars compacta
**SNr:** substantia nigra pars reticulata
**STN:** subthalamic nucleus
**VA/VL:** ventral anterior/ventral lateral nucleus.

## Brain hemisphericity

Brain hemisphericity is based upon the finding that the human brain has been described as an asymmetric entity. (78, 79) However, the precise relationship between the brain's asymmetric design and the functional control managed by each hemisphere remains a controversial subject. As to how much each hemisphere may function is deemed to relay upon its afferent stimulation from the periphery in addition to nutrient and oxygen supply. Current theory holds that hemisphericity is expressed in cortical modulations of the autonomic nervous system, sensory perceptions, cognitive, attentional, learning, and emotional processes. (80) Suggestive evidence

was provided in a study of male adolescents of North American native ancestry subjected to a regimen of processing consonant-vowel combinations (CVs) and musical melodies. A laterality index suggested left hemisphere involvement for melodies and more for CV processing. (81) A further hint was provided in a study of normal young women compared to normal young men within a setting that emphasised hypnosis and partial sensory deprivation.

In these surroundings, the women's reporting of a significantly stronger experience of a 'presence' correlated with their higher score on Vingiano's right hemisphericity questionnaire. (82) Corroboration was offered by Lazure's finding in a questionnaire administered to 50 boys and girls in grades 9 and 12 that a lower self-esteem score obtained on the Rosenberg questionnaire was associated with greater right hemisphericity, as measured by the Vingiano scale (r=0.52). (83)

It has been suggested that an abundance of right- and left-sided structures in the brain besides the cortical hemispheres may be subject to asymmetric function. These would include the thalamus, amygdala, hippocampus, caudate, basal ganglia, substantia nigra, red nucleus, cerebellum, brainstem, and nuclei. To this assortment of structures might be added the peripheral nervous system.

It has been further proposed that hemisphericity could lead to the dysfunction of major systems of the body, including the spine. Hemisphericity of the latter would include subluxation, spinal stiffness (increased extensor tone), spondylosis, intrinsic spinal weakness (decreased postural tone), decreased A-P curves in the cervical and lumbar spine, increased A-P curves in the thoracic spine, increased postural sway in sagittal or coronal planes, and pelvic floor weakness. (6)

## Effects of modalities upon neuroplasticity and neurogenesis

These interventions are built on the premise that functional synaptic connections are built involving cortical and subcortical (striatal and cerebellar) structures, following exposure to a variety of motor experiences. The connections are proposed to be highly dependent upon sensory information. (84)

### *Rehabilitation*

This approach addresses specific areas that are affected by a neurological deficit leading to over- or under-activation. The focus is upon the root cause rather than symptoms and includes the following forms suggested by one clinic specialising in functional neurology: (85)

*Optokinetic (eye movement) exercises:*

A trial involving patients with left-sided chronic neglect (impaired or lost ability to react to or process visual, auditory, tactile, or olfactory sensory stimuli) subjected to repetitive optokinetic stimulation with active pursuit eye movements (R- OKS) compared to a cohort undergoing conventional visual scanning (VST) revealed superior effects experienced by those in the former group in all tasks (digit cancellation, visuoperceptual and visuomotor line bisection and visual size distortion). (86) A larger randomised trial of healthy subjects found that those subjected to OKS exposure for five consecutive days displayed significant reductions of visual dependency, both at a perceptual and postural level, compared to a nonintervention control group. (87) A more elaborate follow-up clinical trial conducted by the same lead author found that patients

with a clinical diagnosis of a peripheral vestibular disorder or chronic dizziness and/or unsteadiness responded positively to a more economical unsupervised DVD that provided an optokinetic rotating disc or drum, but only for vestibular-visual vertigo, and autonomic symptoms. Posturography and functional gait assessments were superior for groups trained with a full-field visual environmental rotator or supervised cohorts. In any case, optokinetic training provided improvements to individuals experiencing peripheral vestibular disorders. (88)

*Balance and coordination therapy:*

The goal of this intervention is to provide a balance board or platform in order to increase the activation of the cerebellar structures controlling posture, head and eye yoked movements, and core stability. Support for this approach was offered by Rhyu, who analysed brain MRI scans of 16 male professional speed skaters, comparing those to scans of 18 non-skaters who did not engage in regular exercise. Skaters were shown to possess larger right hemispheres of the cerebellum and vermian lobules VI-VII (the lobes connecting the left and right parts of the cerebellum) than non-skaters, suggesting that the specialised abilities of balance and coordination in the skaters were associated with flexibility in the cerebellar structures.

Specifically, the balance on the right foot required of speed skaters activated the right lobes of the cerebellum, in addition to the effects of learning a visually guided task believed to occur in the right side of the brain. (89) A second investigation involving traumatic brain injury patients found that balance training using PC-based portable balancers with real-time visual feedback induced plastic improvements in balance control which were associated with alterations in the cerebellar white matter microstructure. (90)

Elsewhere, patients with cerebellar ataxia who participated in a home-based balance exercise program displayed significant rehabilitative improvements that were retained in most outcome measures one month later. (91)

*Complex movement exercises:*

Because specific movements are targeted to specific areas of the brain, exercises which activate areas of the brain that are deficient or over-activated are indicated as a component of functional neurology rehabilitation. Intensive training, for example, is known to produce functional and structural neuro-adaptations. Professional handball players, for instance, displayed an increase in grey matter volume in hand areas, while ballet dancers revealed increases of the grey matter area in foot areas. Fractional anisotropy of the corticospinal tract (FA), on the other hand, showed lower FA in fibres connecting the foot compared to the hand areas of ballet dancers, while handball players revealed lower FA in fibres connecting the hand compared to their foot areas. (92)

A separate investigation involving young adults aged 21-26 revealed modulations of the average activity in the alpha and beta frequencies in EEG patterns of the frontal and central brain regions when subjected to walking conditions combined with a cognitive or motor interference task, indicating an increased cognitive load during the walking In other words, impaired motor performance during dual-task walking was reflected by neural activation patterns of the brain. (93)

After the acquisition of visual motor skills in yet another trial, participants experiencing exercise regimens displayed improvements in procedural memory, but those increases diminished with increasing time lapses between the exercise and acquisition. (94)

A fourth investigation found that moderate dancing activity compared to a non-sedentary control cohort without any dancing experience failed to display significant differences in four

cognitive domains or brain volume, suggesting that a critical level of physical activity and fitness may have been attained in the control group. (95)

*Vestibular rehabilitation:*

The vestibular system (inner ear and cerebellum) are the target areas of this aspect of functional neurological rehabilitation. Included in this type of therapy are a variety of forms of stability exercises, patterned movements of the extremities, rotational forms of movement, and eye exercises. (85)

A systematic review of 9 randomised controlled trials of varying quality revealed positive results in favour of vestibular rehabilitation regarding postural control, functional capacity, and quality of life in an elderly and middle-aged population with complaints of vestibular syndrome, lightheadedness or dizziness. Despite the fact that four studies were rated to be of adequate quality according to the PEDRO scale, they were subject to bias since they did not present allocation concealment or blinding of participants, therapists, or assessors. (96)

In a nonrandomised controlled trial with 20 patients diagnosed with vestibular diseases, cervical manual therapy and shoulder girdle exercises together with head movements, eye coordination tasks, and overall body movements and balance tasks produced improvements in quality of life, postural balance, and intensity of dizziness.These improvements were not associated with pharmacologic treatment. (97)

A novel approach was offered by a team of investigators from Laval University, who determined that the presentation of virtual reality treatments of at least 150 minutes of cumulated exposure ensured symptom improvements in patients with vestibular disorders. The effect was dose-dependent and was based upon the Dizziness Handicap Index and perception of handicap symptoms. (98) A review of the literature led Lacour and Bernard-Demanze to propose a series of general recommendations regarding the timing, type, intensity, and duration of vestibular rehabilitation therapy. They proposed that: (99)

a. Therapeutic progression must proceed from the head to locomotion in a top-down sequence of exercises.
b. The therapy must address all facets of the vestibular syndrome; i.e., the postural, oculomotor, and perceptive symptoms following vestibular injury.
c. Prior to the therapy, nausea, vomiting, and vertigo need to be stopped or reduced.
d. Antiemetics and anti-vertigo drugs might be useful in the early (2-3 day) stage after vestibular injury but must be stopped thereafter.
e. Regaining eye motion control and eye-head coordination are the primary goals of the therapy.
f. Sensory substitution and sensory addition are tools for compensating vestibular loss.
g. Recovery of balance control and gaze stabilisation is attained differently among patients; therefore, a stereotyped vestibular rehabilitation protocol is to be avoided.

*Developmental disorder rehabilitation:*

Areas of the brainstem which are origins of such developmental disorders as Autism Spectrum Disorders, ADHD, learning disabilities, and dyslexia may be targeted for rehabilitation approaches based on the principle of neuroplasticity. Treatments could include eye movement exercises, tracing therapy, complex movement exercises, hand-eye coordination exercises, music therapy,

light stimulation, or balance or coordination work. In animal models, a large body of research has demonstrated the effects of environmental enrichment on both brain and behavioural development. Specific indicators have included the weight and thickness of the cortex, the density or affinity of neurotransmitter receptors, and increased numbers of synapses as well as the density of dendritic branching.

The literature has extended to aberrant genes coding for defective neurotransmitters and receptors in the brain leading to disorders of the synapse in autism, raising the possibility that interactions with environmental factors may influence these components and susceptibility to autism. (100)

A closer inquiry into brain anatomy and the ability to learn nonnative speech sounds found that faster phonetic learners appeared to have more white matter in parietal regions of the brain, particularly in the left hemisphere. The authors concluded that morphological correlates of phonetic learning were related to the ability to process rapid temporal variation. (101) Further support of the neuroplastic responsiveness of the brain to interventions addressing developmental disorders was provided in a study of children with dyslexia. After training, performance on both oral language and reading tests significantly improved, bringing the dyslexic readers' scores into the normal range. At the same time, increased metabolic activity was found in fMRI scans in the left hemisphere language regions, bringing brain activation in these regions closer to that seen in normal children with normal reading skills. (102)

Virtually the same results were obtained in a second study involving dyslexic adults, likewise demonstrating how an external intervention (phonological training) produced increased fMRI signalling in the left hemisphere regions which are engaged by normal readers. (103) Results such as these have led researchers to introduce a cognitive training regimen as a treatment option for ADHD, called Online Neuroplasticity-based Training for the Remediation of ADHD in Children (ONTRRAC), currently under evaluation in a randomised controlled feasibility-efficacy trial. (104) Indeed, a similar brain-computer interface training program for adults with chronic hand hemiplegia after stroke has been shown in 3 patients to increase performance (moving a cursor on a screen) while enhancing MRI images reflecting the modulation of cortical activity, as demonstrated in Figure 11: (105)

### *Manual medicine (spinal manipulation and cranial therapy)*

Nearly 40 years ago, Korr proposed that biomechanically induced deformations of spinal nerves in spinal manipulation could alter axonal transport and with it, trophic influences upon target and effector cells. (106) Analgesia produced by stimulation of neurons outside the customary dermatomal and myotomal distributions used in musculoskeletal diagnosis has been labeled noxious inhibitory control. (107)

The experiments of Sato and Swenson in rats showed that manual therapy could trigger changes in sympathetic function with the potential to alter pain through the sympathetic nervous system's ability to change afferent input. (108) In healthy humans, diversified cervical adjustments appeared to result in parasympathetic responses seen to dominate the LH/HF ratio in heart rate variability measurements, whereas thoracic adjustments led to a reduction of pulse pressure suggesting a sympathetic response. (109) Depending upon which whether the ipsilateral or contralateral side is treated by manipulation and the cortical hemisphericity of the patient, an increase or decrease in brain function has been reported. (17) From these findings, it could be established that manual therapy activates endogenous analgesia systems.

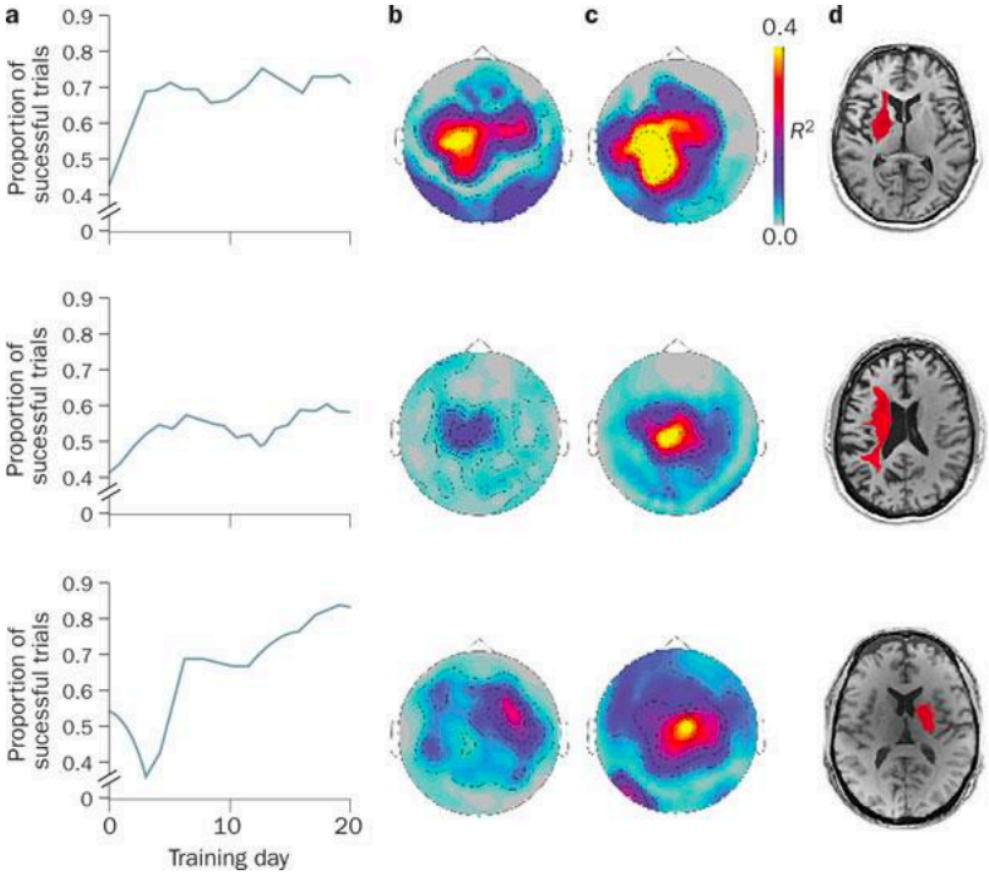



Figure 11: Modulation of cortical activity in stroke patients by brain-computer interface training. Patients with chronic hand hemiplegia after stroke were trained to move a cursor on a screen via modulation of ipsilesional sensorimotor μ rhythm, which was recorded by magnetencephalography.
Successful trials lead to the brain-computer interact opening or closing the patient's paralysed hand via a mechanised orthosis.
(a) The performance of three patients across sessions indicates that the proportion of successful trials increased over time. The statistical maps for the correlations between sensorimotor μ rhythm amplitude, which was recorded from the sensors above the ipsilesional primary motor cortex, and successful performance at (b) early or (c) late training time points demonstrates modulation of sensorimotor rhythm with brain-computer interface training.
Red and yellow colours identify areas where there was a high degree of correlation. d Single axial images from T1-weighted, high-resolution MRI scans obtained from each patient. Each patient's lesion is highlighted in red.

Cranial sacral therapy, on the other hand, assumes that:

1) The human brain pulsates unrelated to heart rate at about 10-14 cycles per minute.
2) A person can feel these pulsations with one's fingertips at given locations on the body.
3) The craniosacral system (cranium, joints, sutures, and sine) can move and be moved by touching and massaging.
4) Restrictions of the natural movements of the cranial system restrict or prevent the flow of cerebral spinal fluid.
5) Persons with increased inflammatory levels and neurological activation, such as with Autism Spectrum Disorder, experience restrictions that create learning disabilities, autistic symptoms (such as behavioural problems, poor social relationships,

communication difficulties, and poor abstract thought), and other social and intellectual abnormalities.

6) With a pressure of about 5 grams, therapists can remove restrictions and generate movement of the cranial system that results in improved functioning.

A publication from the Cambridge Centre for Behavioural Studies in 2011 concluded that the conceptual foundations upon which craniosacral therapy was based '*have been shown to be flawed and are not substantiated by medical science. Its effectiveness in improving problems to which it has been applied has not been proven scientifically*'. (110) More recent publications, however, beginning with a systematic review of 7 studies to assess the benefits of craniosacral therapy, (111) have arrived at a substantially more sanguine conclusion. A study of heart rate variability, for instance, found that patients with subjective discomforts treated with craniosacral therapy displayed increases of standard deviations of all RR-intervals as well as the total power of RR-interval variability in a given frequency range, indicative of a favourable effect of test subjects' autonomic nervous system activity compared to untreated controls. (112)

Furthermore, a survey of patients with Autism Spectrum Disorder published in 2017 disclosed positive responses from therapists, parents, and clients, establishing a basis for conducting further research addressing this encouraging result. (113) Within the space of just 6 years, further positive responses to craniosacral therapy were reported for patients with chronic neck pain, (114) chronic low back pain (the latter two investigations being randomised sham-controlled trials), (115) migraine headache, (116) and anxiety and depression in patients with fibromyalgia. (117)

The previous conclusion that craniosacral therapy lacks a foundation or scientific evidence to affect patient responses or influence the nervous system (110) thus appears to be premature.

### *Acupuncture*

Documentation of the relationship of neuroplasticity to acupuncture has reached the point at which an entire issue of the journal Neural Plasticity has been dedicated to that single topic. (16) Pathologies of a variety of disorders, such as stroke, Alzheimer's disease, and pain are related to neural plasticity. The fact that these conditions have been documented to be relieved by environmental stimulation, as will be illustrated by the following examples, simply underscores the connection between acupuncture and neuroplasticity.

1) Stroke: In a comparison of 28 right-hemispheric stroke patients and 20 healthy subjects undergoing functional magnetic resonance imagining, stroke patients revealed a decreased functional connectivity between the bilateral motor cortices compared with healthy subjects. The decreased functional connectivity was significantly enhanced after acupuncture at the GB34 point, the most significant active point during the left passive thumb-to-index task. The result was thought to shed light upon the mechanism of neural plasticity for acupuncture therapy. (118) In a rat model of ischemic stroke produced by occlusion of the middle cerebral artery inducing cognitive deficit, lesions could be found by MRI analysis in the cortex, hippocampus, corpus striatum, and thalamus regions, accompanied by learning deficits in a water maze and reductions of the dendritic density in the spine and of synapses in the hippocampal pyramidal cells.. Electroacupuncture at the DU20 and DU24 acupoints reversed all of these changes, as well as increases in mRNA/LIMK1 signalling. It was apparent from these data that the mRNA/LIMK1

signalling mechanism was involved in the electroacupuncture-induced hippocampal synaptic plasticity, contributing to improving the learning and memory during the recovery stage of ischemic stroke in this animal model. (119)

2) Experimental spinal cord injury: After spinal cord injury was induced in experimental rats, the motor function of the hind limb was suppressed together with the level of a protein (neurotrophin 3 [NT-3]) essential to neuron survival and growth. Electroacupuncture at the Dazhu (GV 14) and Mingmen (GV acupoints, judged in Traditional Chinese Medicine to stimulate Yang meridians, restorations of both hind limb function and NT-3 levels were found. The conclusion was that the acupuncture treatment promoted neuronal function recovery which could have resulted from upregulating the expression of NT-3.120
3) Renal sympathetic activity: In experimental rats, daily acupuncture at the LR3 acupoint for 2 weeks attenuated increases of mean blood pressure that had previously been caused by enhanced renin release. It also increased the ratio of the low-frequency component compared to the high-frequency component in heart rate variability measures while reducing kidney epinephrine and norepinephrine, indicating the reduction of renal sympathetic activity. (121)
4) Pain memory: In yet another rat experimental model, electroacupuncture at the bilateral acupoint ST36 alleviated the retrieval of pain induced by the injection of carrageenan, while the NSAID drug indomethacin did not. Injection of a protein kinase (PKA) inhibitor into the anterior cingulate cortex likewise blocked the retrieval of pain memory. Electroacupuncture reduced the activation of PKA together with cyclic AMP (cAMP) and the signalling protein CREB. It thus appeared that electroacupuncture's suppression of pain memory could be attributed at least partially to the inhibition of the cAMP/PKA/CREB signalling pathway. (122)
5) Downregulation of NMDA receptor: Previous data had shown that the N-methyl-d-aspartate receptors (NMDARs) are responsible for the glutamate-induced excitotoxicity in the postischemic brain. Expression of a subunit (NR1) of the NMDAR has been shown to be suppressed by electroacupuncture in a rat model of ischemic stroke, whereas a component of the cell signalling pathway (TrkA) leading to nerve growth factor, critically involved in cell survival and neuroprotective effects, is upregulated. These two factors may be components of the neuroplastic effects of acupuncture in alleviating stroke symptoms. (123)
6) Neuroplasticity changes in the human motor cortex: An acupuncture session involving 10 acupoints produced changes in potential amplitude measured by transcranial magnetic stimulation from both the ipsilateral and contralateral hemispheres compared to baseline. Thus, corticomotoneuronal excitability and interhemispheric competition could be modulated by acupuncture therapy in healthy subjects. (121)

### *Biofeedback*

Biofeedback is another mechanism by which environmental stimulation can be utilised to take advantage of the neuroplasticity that characterises human nervous systems. Whereas training and learning could involve numerous mechanisms and areas of the brain affected, biofeedback targets only a specific region of the brain, and thus permits insight into that specific area and how it contributes to behaviour. Several lines of evidence demonstrated the efficacy of biofeedback and its relationship to neuroplasticity:

1) Inductions of activity patterns achieved with a decoded functional magnetic resonance imagining (fMRI) signal as an online feedback method were able to accomplish the induction of activity patterns in the visual cortex of healthy adults. This indicated that the adult early visual cortex was so plastic that mere repetitions of the activity pattern corresponding to a specific feature of the cortex was sufficient to produce visual perceptive learning of a specific orientation, even without
    i. presentation of the stimulus
    ii. conscious awareness of the meaning of the neural patterns that subjects induced, or
    iii. knowledge of the intention of the equipment utilised. (124)
2) A second trial, also using fMRI based neurofeedback using blood oxygenation signals from a circumscribed region of interest in the brain demonstrated that participants showed enhanced perceptual sensitivity only if they had undergone the previously learned regimen, and only for that region of the visual cortex. (125) Both studies thus demonstrated a causal relationship between the altered activity in the early visual cortex and the observed behavioural changes. (126)
3) A third investigation employing electroencephalogram (EEG) biofeedback administered to post-cancer patients with cognitive impairments showed reductions of the negative cognitive impairments and emotional sequelae of cancer treatment, in addition to improving fatigue and sleep patterns. (127)
4) Elsewhere, a neurofeedback training protocol designed to improve sustained attention induced increases of fractional anisotropy in white matter pathways and of the volume of gray matter in cerebral structures involved in the types of increased auditory and visual attention achieved. The authors reported that, after 50 years of research in the field of neurofeedback, this was the first empirical demonstration that neurofeedback training could lead to microstructural changes in white and gray matter. (128)
5) A Cochrane review of 13 trials involving 269 people subjected to electromyographic biofeedback showed a small amount of evidence suggesting that the procedure had a beneficial effect when used with standard physiotherapy techniques. Some studies, however, found no effect. (129)

### *Aromatherapy*

With its use of essential oils from plants, aromatherapy is postulated to work by stimulating olfactory receptors in the nose, communicating with the amygdala and hippocampus in the brain which controls emotions and memories. Aromatherapy also acts through the skin.

1) The presentation of three different odorants (spiced apple, eucalyptus, and lavender) to subjects produced widely differing alpha and theta activity of the electroencephalographic (EEG) patterns in the left and right hemispheres. These did not agree with self-reports registered on questionnaires, indicating that the perceptual component of olfaction accounted for a limited part of the central nervous system changes produced by smelling an odor. (130)
2) Valeric acid (rated as unpleasant) and phenylethyl alcohol (rated as pleasant) were rated as to their effects upon the EEG frequency bands theta, alpha 1, alpha 2, and beta 1 at eight locations. Within 8 seconds after stimulus release, valeric acid increased alpha 2

power whereas phenylethyl alcohol did not. These data indicated that smelling an unpleasant odor led to a cortical deactivation. (131)

3) A 1.5-2.5-fold increase in relative sympathetic activity, representing the low frequency amplitude of systolic blood pressure, was produced in humans by the fragrance inhalation of essential oils, such a pepper oil, estragon oil, fennel oil, or grapefruit oil. On the other hand, the fragrance inhalation of rose oil of patchouli oil produced at 40% decrease in relative sympathetic activity. Inhalation of the odorless solvent triethyl citrate caused no change. Inhalation of pepper oil also caused a 1.7-fold increase in plasma adrenaline concentration, while the fragrance inhalation of rose oil led to a 30% decrease of the adrenaline levels. Thus, it was apparent that fragrance inhalation of essential oils could modulate sympathetic activity in adults. (132)
4) An early component (at 400-1000 ms) of the beta wave variation, part of an EEG method of measuring the slow brain waves (>13 Hz) at the front of the scalp, was identified as responsive to odor while nearly independent of the subject's psychological state, degree of arousal, sex, age, or level of consciousness. (133)
5) Elsewhere, inhalations of a variety of fragrances by healthy volunteers showed that prolonged inhalations of fragrances influenced autonomic nervous system parameters (as shown by systolic and diastolic blood pressures) as well as mental and emotional conditions. In addition, the chemical chirality of the odor molecules limonene and carvone produced differing physiological responses. (134)
6) In percutaneous artery intervention patients in an intensive care unit, aromatherapy oils effectively reduced their anxiety levels and increased the sleep quality, although blood pressure levels were not significantly affected. (135)

### *Functional neurology massage*

Using learning and feedback principles of neuroplasticity, functional neurology massage seeks to produce an improved congruence of the body, its emotions, and the nervous and endocrine systems. Unlike conventional massage, functional neurology massage may employ eye movements, aromatherapy, standing single leg exercises, massage to one side of the body, or light touch bodywork. (136) The purpose is to engage the nervous system, in which several lines of evidence either directly or indirectly suggest a neuroplastic response to massage:

1) A study of healthy adults subjected to pressure massage tracked the high- and low-frequency components (HF and LF) of heart rate variability as well as the LF/HF ratio as noninvasive markers of the autonomic nervous system. An increase of the HF ratio after moderate pressure massage suggested increased vagal efferent activity, while the decrease in the LF/HF ratio implied a shift from sympathetic to parasympathetic activity. Interestingly, light pressure massage produced precisely the opposite results. (137)
2) A combined regimen of massage and stretching in fibromyalgia patients after 18 sessions produced an increase of parasympathetic and decrease of sympathetic tone shown by heart rate variability. Joint flexibility also improved significantly. (138)
3) Similar results were found in children hospitalised in an intensive care unit. Foot and hand massage of 18 children produced a significant increase of parasympathetic activity as seen with a greater increase of HF compared to LF. Interestingly, the sum of HF + LF was positively correlated with clinical severity. (139)

4) The combined application of heat and massage for 40 minutes daily, 5 days a week for 2 weeks in 139 healthy subjects led to a significant increase of latency of a sympathetic skin response test, Plasma cortisol and norepinephrine levels also registered significant decreases, the sum total of indicators suggesting a relaxation of the autonomic nervous system. (140)
5) A more direct effect of massage was found with rats following facial nerve transection and immediate microsurgical repair. Those animals receiving 5 minutes of daily massage to the left whisker pad throughout the recovery period showed improved functional recovery in all whisking parameters compared to controls. In other words, massage produced an accelerated recovery. (141)
6) A similar investigation of the rat transected facial nerve model should that gentle stroking of the paralysed facial muscles resulted in full recovery of function, whereas electrical stimulation failed to improve vibrissal motor performance. (142)

### *Yoga*

Yoga is linked to neuroplasticity through habituation of the posture, breathing, guided imagery, and meditation that characterise this rapidly growing practice. It is essentially a training of the brain to focus as well as process positive thoughts, leading to activation of the parasympathetic nervous system with deeper breathing. The combination of breath control, posture, and presence practiced in yoga encourage a linkage between neural pathways, creating strong and complex neural networks, giving rise to the popular expression, '*Neurons that fire together, wire together*'.

Deep breathing, music, physical activity, communal experience, and music experienced in yoga stimulate the reward system characterised by dopamine and endorphin release which further amplify states of healing and well-being. Specific examples of the neuroplastic and neuro-protective effects of yoga include:

1) A study with non-suicidal outpatients of depression offered yoga showed correlated decreases of the Hamilton Depression Rating Scale and increase in serum brain-derived neurotrophic factor. These effects were not seen in groups receiving antidepressants alone or in combination with yoga. The conclusion was that neuroplastic mechanisms could be related to the therapeutic mechanisms of yoga in cases of depression. (143)
2) Yoga mediation practitioners were shown in another study to possess greater grey matter volume in frontal, limbic, temporal, occipital, and cerebellar regions compared to a matched control group. A dose-dependent effect was shown by the correlation of grey matter volume with the duration of yoga practice. Furthermore, the yoga practitioner group showed significantly fewer cognitive failures on the Cognitive Failures Questionnaire. From these results, it appeared that hatha yoga practice could be associated with the promotion of neuroplastic changes in executive brain systems, which could confer therapeutic benefits that accrue with repeated practice. (144)
3) Essentially the same result was obtained in a second study, in which subjects lacking yoga experience displayed the well-documented age-related global brain grey matter decline, while individuals taking yoga did not. Again, there was a dose-dependent correlation of years of yoga experience with grey matter volume differences in the left hemisphere (frontal operculum and orbital cortex), suggesting that yoga tuned the brain toward a parasympathetically driven mode and positive states. The combination of postures and meditation contributed mostly to the size of the hippocampus, precuneus/

PCC, and S1/SLP, while the combination of mediation and breathing exercises contributed the most to V1 volume. The neuroprotective effects of yoga were suggested to provide a neural basis for its beneficial effects. (145)

4) In type 2 diabetic subjects aged 30-60 years, numerous types of yoga exercises conducted for 30-4 minutes every day for 40 days led to an increase of right hand and left hand median nerve conduction velocity, while the same parameters of the control groups deteriorated over the period of study. A neuroprotective role of yoga against the progressive decay of nerves in diabetes 2 was suggested by these data. (146)
5) In a randomised controlled trial, individuals engaged in yoga breathing compared to control subjects displayed an induction of salivary nerve growth factor, a trophic factor involved in the development, maintenance, and survival of the peripheral nervous system and cholinergic neurons of the central nervous system. (147)

### *Cognitive exercises, visualisation therapy, guided imagery*

Batteries of appropriately designed exercises encourage the creation of new synapses and neural circuits, a manifestation of the neuroplasticity thought to characterise areas of the brain. These approaches fall under the headings of cognitive exercises, visualisation therapy, or guided imagery.

Among the exercises and actions suggested to increase cognitive ability are 8 proposed by Bergland:

i. physical activity
ii. openness to experience
iii. curiosity and creativity
iv. social connections
v. mindfulness mediation
vi. brain-training games
vii. sufficient sleep, and
viii. reduction of chronic stress. (148)

In terms of guided imagery, several investigations shed light upon the ability of such measures to promote neurological activity:

1) Perceptions of a visual cue stimulus were found to modify oscillations in the sensorimotor areas specific to hand movements as monitored by EEG patterns. (149)
2) Cued motor imagery enhanced motor evoked potentials of selected muscles in both healthy and stroke-affected individuals. Visual cueing was most effective in young people (20-35 years), while auditory cueing was most effective in both healthy and stroke-affected older people (over 55 years). (150)
3) A study of healthy volunteers revealed that an application of guided imagery and music stimuli produced increased activation seen by fRMI in five neural regions associated with negative emotional and episodic memory processing. Regions of the brain included the

left amygdala, left anterior cingulate gurus, left insula, bilateral culmen, and left angular gyrus. (151)

4) Based on the hypothesis that neuropathic pain after spinal cord injury was based on a mismatch between motor commands and sensory feedback, investigators recruited five paraplegic patients to see whether a visual illusion aimed to correct this mismatch reduced pain. Guided imagery produced a slight reduction of pain, but not as great as that achieved by exposure to a mirror in which patients were exposed to virtual walking consisting of a mirror and a film of lower body walking. (152)
5) A six-week training in mental imagery for upper limb amputees produced significant reductions in the intensity and unpleasantness of constant pain and exacerbations. This was accompanied by reductions of cortical reorganisations of motor and somatosensory cortices expanding from the lip area to the hand area, as seen by fMRI. (153)
6) Interestingly, individuals who were hypnotised experienced the loss of autonomic (heart rate, respiratory frequency, tonic skin resistance, EEG patterns) responses expected during guided imagery that was considered to be neutral. However, the emotional valence of imagery that was judged to be unpleasant overrode the apparent hypnotic block, such that subjects exposed to such imagery experienced changes in the gamma, beta2 and beta 3 activities as well as in heart rate and respiratory frequency. (154)

### *Eye muscle exercises (Vision Therapy)*

The purpose of vision therapy is to improve visual abilities by training the eyes and brain to work together more effectively. Chinese eye exercises, in particular, were developed as a form of massage around peri-ocular acupoints and grounded in theories of traditional Chinese medicine.

1) Eye acupressure was believed to improve neural nutrition to the eyes, reducing eyestrain and the possibility of myopia as well as preventing migraine, neuralgia of the trigeminal nerve, conjunctivitis and facial paralysis. (155)
2) More recently, 190 schoolchildren aged 10-14 years underwent standard Chinese eye exercises and experienced a reduction in accommodative lag (ability to accommodate near and distant targets) in the short term compared to those who performed sham point eye exercises. It was unclear, however, whether such exercises were sufficient to prevent myopia progression in the long term. (156)
3) Exercises directed at accommodation, vergence, and convergence produced vergence and accommodation improvements in the vergence exercises only. (157)
4) Yogic eye exercises, consisting of palming, blinking sideways viewing, front and sideways viewing, rotational viewing, up and down viewing, preliminary nose tip gazing, and near and distant viewing, significantly reduced eye fatigue on a group of undergraduate nursing students. (158)
5) In terms of cognitive abilities applied to attention and memory, healthy volunteers subjected to rapid serial visual presentations showed greater accuracy in responding to target letters separated by one distractor, as well as in letter identification if they performed active eye exercises consisting of following a white square on a black background while making saccadic eye movements for 18.5 minutes. (159)
6) Elsewhere, a prospective randomised controlled trial found that patients with idiopathic cranial nerve VII paresis experienced a greater rate of recovery if they underwent eye

exercises for a period of four weeks with improvements in oribicularis occuli muscle strengths. (160)

7) Evidence supporting the efficacy of eye exercises in managing convergence insufficiency, improving visual field remnants after brain damage, and developing fine stereoscopic skills was supported in a systematic review in 2005. (161)

### *Meditation*

Mindfulness meditation, defined by Jon-Kabat Zinn as '*the ability to pay total attention to the present moment with a nonjudgmental awareness of the inner and/or outer experiences*', (162) raises an interesting paradox. Despite casual impressions, mediation actually appears to the neuroscientist as a complex task, involving what appear to be the contradictory tasks of intense concentration and openness to sensory experiences, emotions, and thoughts. Accordingly, meditation processes have been divided into those engaging focused attention (FA) and those involved in open monitoring (OM). FA, therefore, devotes full attention on a given object in a sustained fashion, while OM maintains an awareness of the content of experience from moment to moment, recognising emotional and cognitive patterns.

Specific neural networks and instances supporting the occurrence of neuroplasticity are described as follows:

1) Activation of the dorsolateral prefrontal cortex, associated with executive decision making and attention, has been reported across a variety of mediation styles. Increased activation in the cingulate cortex, which plays a major role in integration of attention, motivation, and motor control, has also been noted, as has the activation of the anterior insula involved with the perception of visceral feelings (hunger, thirst, balance, detections of heart and breathing rates). (163)
2) In FA meditation, expert meditators with an average of 19,000 hours of practice showed more activation in a network of brain regions typically involved in sustained attention. However, expert meditators averaging 44,000 hours had less activation in response to distractor sounds used to probe the meditation. This inverted u-shaped learning curve suggested that, after extensive FA meditation training, minimal effort was needed to sustain attentional focus. Compared to novices, experts had less brain activation in regions related to discursive thoughts and emotion while showing more activation in the regions related to response inhibition and attention. These variations with hours of practice suggested plasticity in these mechanisms. (164)
3) Demonstrations of neural changes during OM meditation was provided by long-term Buddhist practitioners, who registered electroencephalograms with high-amplitude gamma-band oscillations and phase-synchrony during meditation, differing from controls. Specifically, the ratio of gamma-band activity (25-42 Hz) to slow oscillatory activity (4-13 Hz) was initially higher in the resting baseline before mediation for the practitioners compared to controls. During mediation, the difference between the two cohorts increased sharply. (165)
4) Differences in positive and negative responses to emotional sounds as shown by fMRI brain activation patterns of novices compared to experts in meditation are shown in Figure 12 from data from Lutz: (166)

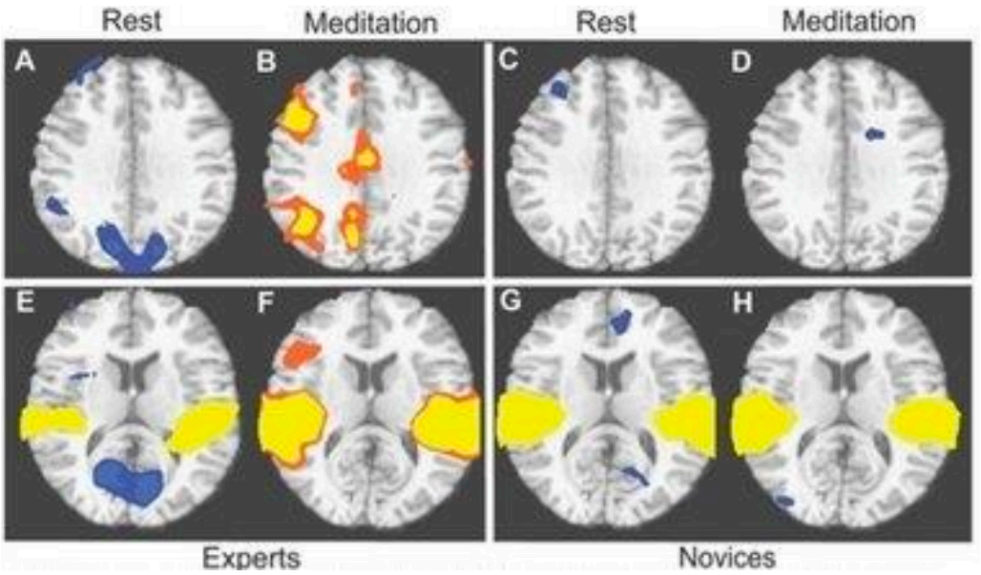



Figure 12: Directionality of brain activation. Areas showing a negative (dark blue) or positive (orange) impulse response on average across 10 seconds in responses to all emotional sounds for 15 novices compared to 15 experts in meditation. Top row (A-D) represents one cross-section at Talalrach coordinate z=3 (a fMRI slice of the brain) and bottom row (E-H) represents another cross-section at the Talalrach coordinate z=13.

5) To assess additional neurological changes during OM mediation an attentional blink test was utilised. It involved presenting two targets T1 and T2 in rapid succession, representing competition between the two targets for limited attentional resources, such that there would be a lack of resources for T2 processing if they were focused upon T1 presented immediately before. After three months of Vipassana OM meditation, the brain-resource allocation to both T1 and T2 was attenuated as shown by diminished P3b amplitudes, suggesting that less elaborate stimulus processing led to the reduced likelihood of 'getting stuck' on a target. (167)
6) A mindfulness stress reduction program conducted over 8 weeks involving meditation in healthy individuals produced reductions of the density of the right basolateral gray area of the amygdala, a part of the limbic system which performs a primary role in the processing of memory, decision-making, and emotion reactions. (168)
7) Increases of gray matter in meditation were apparent from high-resolution MRI patterns of the right orbito-frontal cortex, the right thalamus and left inferior temporal gyrus, and right hippocampus, possibly accounting for the meditators' singular abilities to cultivate positive emotions, retain emotional stability, and engage in mindful behaviour. (169) A second study showed that brain regions associated with attention, interoception and sensory processing were thicker in meditation participants than in matched controls. (170) Higher gray matter density in the lower brain stem of experienced meditators compared with non-meditators was reported elsewhere. (171)
8) Integrative body-mind training, a form of mindfulness meditation, was shown by Tang and coworkers to improve the efficiency of white matter measured by fractional anisotropy in individuals after a 4-week period. It involved increased myelin and other axonal changes, demonstrating white matter neuroplasticity involving the anterior cingulate cortex, a part of the brain network related to self-regulation. (172)

The fact that exercise is intimately related with energy metabolism, it is reasonable to suggest that the alterations of energy-related molecular systems should affect neuronal excitability, synaptic plasticity, and cognition. In addition to the hippocampus, which plays a major role in memory processing, the hypothalamus is a brain region influenced by physical activity. The application of exercises to enhance executive function activities, those involved in planning and selecting strategies that organise goal-oriented actions as opposed to basic information processing, has received strong support in the scientific literature as reviewed by Tomporowski and coworkers, who conducted their own review of correlational and cross-section studies as well as randomised experiments to evaluate the impact of chronic exercise or habitual physical activity on measures of children's mental function. They concluded that gains in children's mental functioning due to exercise training were found mostly on tasks involving executive functions. (173)

An extensive array of structural and molecular indicators promoting neurogenesis, neuroplasticity, and neural integrity that change with exercise have been identified as follows:

1) An increase of gray matter volume and reduced cognitive impairment seen with greater amount of walking. (174) Higher amounts of gray matter tissue density in judo players seen by voxel-based morphometry. (175)
2) Increases of hippocampal volume by 2% with aerobic exercise training, effectively reducing age-related loss of volume by 1 to 2 years. (176)
3) Elevations of dentate gyrus cerebral blood volume, correlated with measurements of neurogenesis and cardiopulmonary and cognitive function. (177)
4) A larger amplitude of ERN, a component of event-related brain potentials (ERPs) which in turn are a class of EEG activity indicative of the synchronous activity of large populations of neurons. This was correlated with greater post-error accuracy of tasks, suggesting increased cognitive flexibility. (178)
5) Increased amplitudes of the P3b peak in higher–fit individuals, an ERP component approximately 300-800 ms following stimulus onset. (179)
6) Elevations of the neuropeptide brain derived neurotrophic factor (BDNF) in the hippocampus (an area vital for learning and memory), in turn driving several molecular signalling systems involved in the metabolism of energy, thus modulating the capacity of the synapse to process information relevant to cognitive functions. This sequence is illustration in Figure 13: (180)

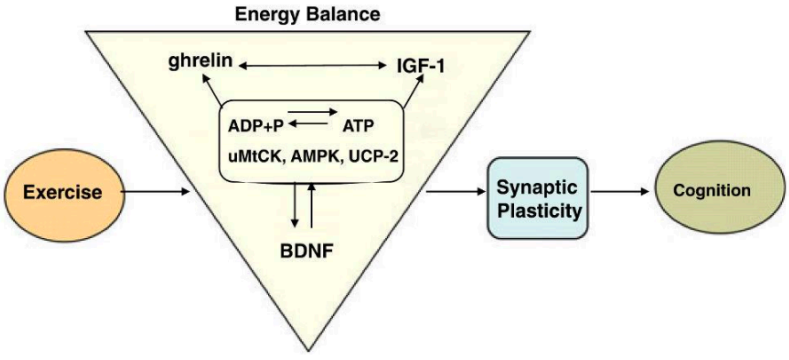



**Figure 13:** Proposed mechanism by which exercise may enhance cognitive function by engaging aspects of cellular energy metabolism. Molecular systems, such as μMtCK (myosin-like chain kinase), AMPK (AMP-activated protein kinase), and UCP-2 (uncoupling protein-2) may work at the interface between energy and synaptic plasticity. IGF-1 (insulin-like growth factor), ghrelin and energy-related molecules can interact with BDNF (Brain-Derived Neurotrophic Factor) to modulate synaptic plasticity and cognitive function. (180)

7) Promotion of insulin-like growth factor 1 (IGF-1) acting in concert with BNDF, shown by the abolition of the ability of exercise to elevate the levels of BDNF mRNA and protein, as well as exercise's capacity to augment recall in experimental rats. Investigators suggested that IGF-1 interfaced with BDNF it mediating synaptic and cognitive plasticity,181 lending further support to the schematic shown in Figure 13. (180)
8) Identification of vascular endothelial growth factor (VEGF) as a necessary component for the effects of running on adult hippocampal neurogenesis in adult experimental mice. (182)

Together with the aforementioned structural and molecular changes have been an abundance of studies that have documented improvements of cognitive performance with exercise. Cognitive improvements have ranged anywhere from animal performance in a maze to human attention, processing speed, and memory, counteracting the degradations associated with increasing age. (183)

In several instances of diseases or disorders, movement through exercise has been associated with the rebuilding of neural responses, lending further evidence to support the link between movement and neuroplasticity and neurogenesis. The common elements include repetition, intensity, cognitive engagement, challenge, skill training, motivation, goal-based practice, and learning through feedback, all leading to improvements in motor performance as well as cognition. (184)

1) In the neurorehabilitation of Parkinson's disease patients: (184)
   a) Interventions have included
      i. treadmill training
      ii. amplitude training
      iii. Tai Chi
      iv. tango dancing
      v. boxing, and
      vi. forced cycling.
   b) These have all been suggested to restore dopamine with the goal of reconstructing deranged circuitry within the basal ganglia.
   c) fMRI studies have shown that the learning of dual task training in the rehabilitation of Parkinson's disease has occurred mainly through compensatory cortical circuits.
   d) Concerning the restoration of depleted dopamine levels in Parkinson's disease, studies have demonstrated that exercise can enhance the vesicular release of dopamine, increasing synaptic occupancy and reducing dopamine clearance. Exercise may also enhance the expression of dopamine receptor.
2) Additional studies with experimental mice have shown that intensive exercise can restore aspects of glutamate receptor expression. Glutamate and its receptors are known to contribute to neuroplasticity and synaptic strengthening during learning, of possible value in the management of Parkinson's disease.
3) Studies in healthy rodents have shown that exercise increases dendritic spine density in various regions, including the hippocampus and cerebellum. (185, 186) Research to determine whether such findings are applicable to human disorders is clearly indicated.

4) An approach to physical rehabilitation called Constraint-induced Movement therapy has been described as having been used 'effectively' in managing stroke, spinal cord injury, fractured hip, multiple sclerosis, and cerebral palsy. (187) Brain reorganisation as seen by fMRI has been reported to accompany this therapeutic approach, although it was not clear whether the changes could be detected more in the lesioned compared to the un-lesioned hemisphere in cases of chronic stroke hemiparesis. (188)
5) Stimulation timing in stroke rehabilitation appeared to be a critical factor in one investigation, demonstrating that the responsiveness of the motor cortex was affected positively by stimulation during the late motor response period and negatively during the early movement period when the stimulation was combined with a robotic reach practice. This indicated that the sensitivity of the activated motor cortex to additional stimulation was highly dynamic. (189)
6) A series of 1 hour Yang style Tai Chi classes with mental imagery conducted twice weekly for 8 weeks with patients with type 2 diabetes led to significant improvements in a variety of functional outcome measures, including Hoffman reflex and sural and perficial peroneal nerve conduction velocity, as well as latency. (190)

### *Diet*

The role of proper diet in maintaining optimal energy metabolism and building materials to the body can be extrapolated without difficulty to the integrity of the neuron, neurotransmitters, and neuroplasticity. Studies of animal and human behaviour and cognition have substantiated the clinical domain of evidence supporting the neuroprotective role of diet, while advances in cell and molecular biology have contributed greatly to conceptualising the constructive roles of diets in promoting neural structure and function.

1) Identification of nutrients of interest: An overall list of beneficial nutrients in the human diet has been provided by Gomez-Pinilla, shown below in Table 1: (191)
2) n-3 Polyunsaturated fatty acids (3-PUFA, omega-3 fatty acids): 3-PUFAs are distributed to nearly every cell in the body with effects on membrane composition and signalling as well as the regulation of gene expression. Indeed, docosahexaenoic acid (DHA) turns out to be the most abundant omega-3 fatty acid in cell membranes in the brain, while at the same time the human body is not efficient in synthesising DHA and therefore must obtain it from the diet. (191) The role of DHA in neuronal membranes, in particular, has been shown to facilitate membrane translocation activation of the phosphatidylinositol 3-kinase (PI (3)K) Akt signaling, a critical pathway in cell survival. It accomplishes this by increasing phosphatidyl serine (PS), the major phospholipid in cell membranes. This has led Akbar and a team of researchers to propose the mechanism of action of DHA at the membrane level as shown in Figure 14: (192)

   DHA-driven increases in PS with accelerated Akt translocation has been reported elsewhere as well. (193)

Table 2: Nutrients found to affect cognitive function

| Nutrient | Effects on cognition and emotion | Food sources |
|---|---|---|
| Omega-3 fatty acids (for example, DHA) | Amelioration of cognitive decline in the elderly[148]; basis for treatment in patients with mood disorders[80]; improvement of cognition in traumatic brain injury in rodents[81]; amelioration of cognitive decay in mouse model of Alzheimer's disease[140,150] | Fish (salmon), flax seeds, krill, chia, kiwifruit, butternuts, walnuts |
| Curcumin | Amelioration of cognitive decay in mouse model of Alzheimer's disease[123]; amelioration of cognitive decay in traumatic brain injury in rodents[89] | Turmeric (curry spice) |
| Flavonoids | Cognitive enhancement in combination with exercise in rodents[92]; improvement of cognitive function in the elderly[151] | Cocoa, green tea, Ginkgo tree, citrus, wine (higher in red wine), dark chocolate |
| Saturated fat | Promotion of cognitive decline in adult rodents[4]; aggravation of cognitive impairment after brain trauma in rodents[88]; exacerbation of cognitive decline in aging humans[3] | Butter, ghee, suet, lard, coconut oil, cottonseed oil, palm kernel oil, dairy products (cream, cheese), meat |
| B-vitamins | Supplementation with B6, B12 or folate has positive effects on memory performance in women of various ages[152]; vitamin B12 improves cognitive impairment in rats fed a choline-deficient diet[153] | Various natural sources, B-12 not available from plant products |
| Vitamin D | Important for preserving cognition in the elderly[154] | Fish liver, fatty fish, mushrooms, fortified products, milk, soy milk, cereal grains |
| Vitamin E | Amelioration of cognitive impairment after brain trauma in rodents[102]; reduces cognitive decay in the elderly[119] | Asparagus, avocado, nuts, peanuts, olives, red palm oil, seeds, spinach, vegetable oils, wheat germ |
| Choline | Reduction of seizure-induced memory impairment in rodents[155]; a review of the literature reveals evidence for a causal relationship between dietary choline and cognition in humans and rats[156] | Egg yolks, soy beef, chicken, veal, turkey liver, lettuce |
| Combination of vitamins (C, E, carotene) | Antioxidant vitamin intake delays cognitive decline in the elderly[157] | C: citrus fruits, several plants and vegetables, calf and beef liver. E: see above |
| Calcium, zinc, selenium | High serum calcium is associated with faster cognitive decline in the elderly[158]; reduction of zinc in diet helps to reduce cognitive decay in the elderly[159]; lifelong low selenium level associated with lower cognitive function in humans[160] | Calcium: milk, coral. Zinc: oysters, a small amount in beans, nuts, almonds, whole grains, sunflower seeds. Selenium: nuts, cereals, meat, fish, eggs |
| Copper | Cognitive decline in patients with Alzheimer's disease correlates with low plasma concentrations of copper[161] | Oysters, beef/lamb liver, Brazil nuts, blackstrap molasses, cocoa, black pepper |
| Iron | Iron treatment normalizes cognitive function in young women[162] | Red meat, fish, poultry, lentils, beans |

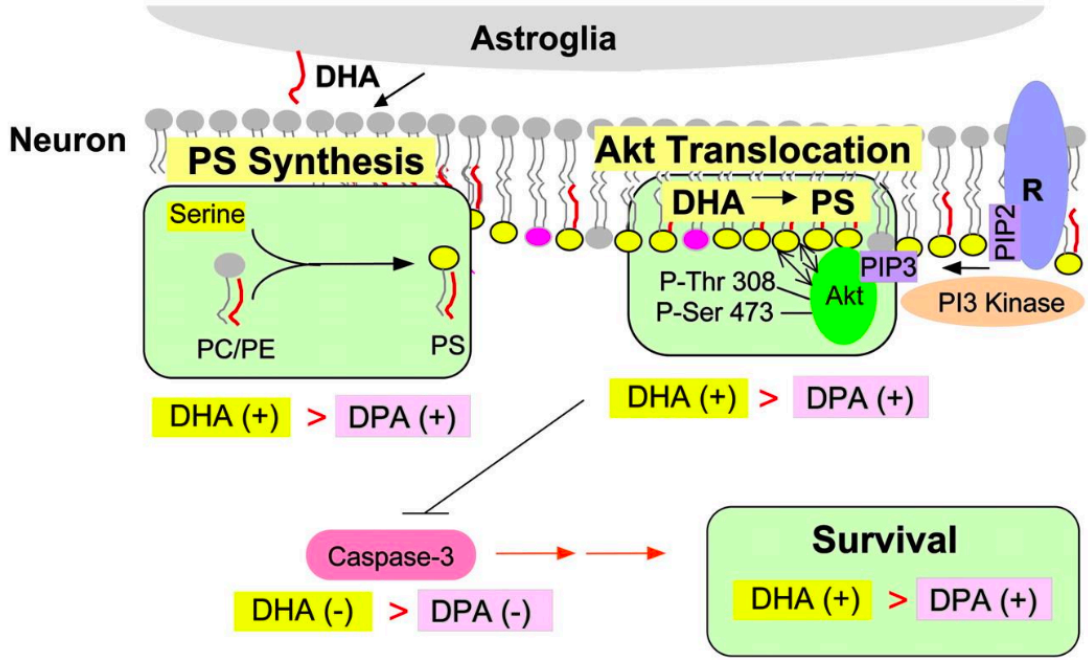



Figure 14: A schematic model of the effect of DHA upon neuronal survival. DHA is provided from astroglia incorporated into neurons and promotes PS accumulation by serving as the preferred substrate for PS biosynthesis. Membrane concentration of PS facilitates Akt translocation through interaction with basic residues in the PH domain, resulting in efficient phosphorylation and activation of Akt and suppressing caspase-3 activation and cell death. This occurs especially under adverse conditions where PIP3 generation is limited. DPA, replacing DHA in n-3 fatty acid deficiency, is not as effective as DHA in promoting PS accumulation and Akt translocation and is consequently less effective in supporting cell survival. DHA = docosahexaenoic acid; DPA = docosapentaenoic acid' PIP3= phosphatidylinositol (3,4,5)-triphosphate; PS = phosphatidylserine; PC = phosphatidylcholine; PE = phosphatidylethanolamine

Beyond the understanding that 3-PUFAs play a critical role in membrane integrity, which would be seen as a factor in neurotransmission and neuroplasticity, is the finding that phospholipids containing high amounts of polyunsaturated fatty acids catalyse reactions which have been shown to hyperpolarise the reactive oxygen species plasma membrane and visual response. (194) This can be seen as a direct effect of 3-PUFAs upon neuroplasticity.

a) To complement the salutary effects of exercise upon neuroplasticity as described above, a trial with experimental rats found that animals receiving 1.25% DHA for 12 days demonstrated significantly enhanced spatial learning effects as well as elevated levels of the neuroprotective BDNF. Levels of the signalling proteins cyclic AMP-response element (CREB_, Akt, CaMKII and synapsin I were increased as well, accompanied by the reduction of hippocampal oxidized protein levels. Clearly, DHA enhanced the effects of cognition and BDNF-related synaptic plasticity. (195)
b) Conversely, diets high in saturated fats decreased the level of BDNF to the extent of compromising neuroplasticity and cognitive function. But if such high fat diets were supplemented with vitamin E, oxidative damage was dramatically reduced accompanied by normalised levels of BDNF, synapsin I, and CREB. (196)
c) Reductions of BDNF, neuronal plasticity, and learning were confirmed in a second trial of rats put on a high-fat, refined sugar diet. (197)
d) Even if normal diets were deficient in 3-PUFAs (in this case α-linolenic acid), both brain DHA and nerve growth factor levels in experimental rats fell to half of those seen in the control groups. Both were restored with the resumption of normal diet. (198)
e) Age-dependent impairments in long-term potentiation, reflected by decreased transmitter release in the hippocampus of aged rats, have been proposed to be the product of increased membrane rigidity. Dietary supplementation of aged rats with omega-3 fatty acids restored the concentrations of both docosahexaenoic acid and arachidonic acid as two primary PUFAs in neuronal membranes. Eight weeks of the omega-3 fatty acids reversed the age-related impairments in long-term potentiation and the release of glutamate transmitter. Thus a link between membrane rigidity, neuroplasticity, and dietary manipulation was established. (199)

### *Botanicals*

A subcategory of dietary additions to be considered as factors affecting neuroplasticity are the polyphenols, such as phenolic acids, stilbenes, lignans, flavonols, and anthocyanins. Some 8,000 compounds of these possess antioxidant properties and have been cited for reducing risks of neurodegenerative diseases and age-related cognitive decline as well as oxidative stress.

Polyphenols have been proposed to exert neuroprotective, neuroplastic, neurogenic, and anti-inflammatory effects. (200) A combination of studies from animal models have suggested that long-term supplementation with flavonoids, in particular, has modulated synaptic plasticity through the activation of neuronal receptors, signalling proteins (kinases), and gene expression. Human clinical studies have suggested that flavonoids, can positively affect peripheral and cerebrovascular blood flow, an indirect method by which flavonoids could affect brain health and cognition.

These pathways are shown in the schematic in Figure 15: (201)

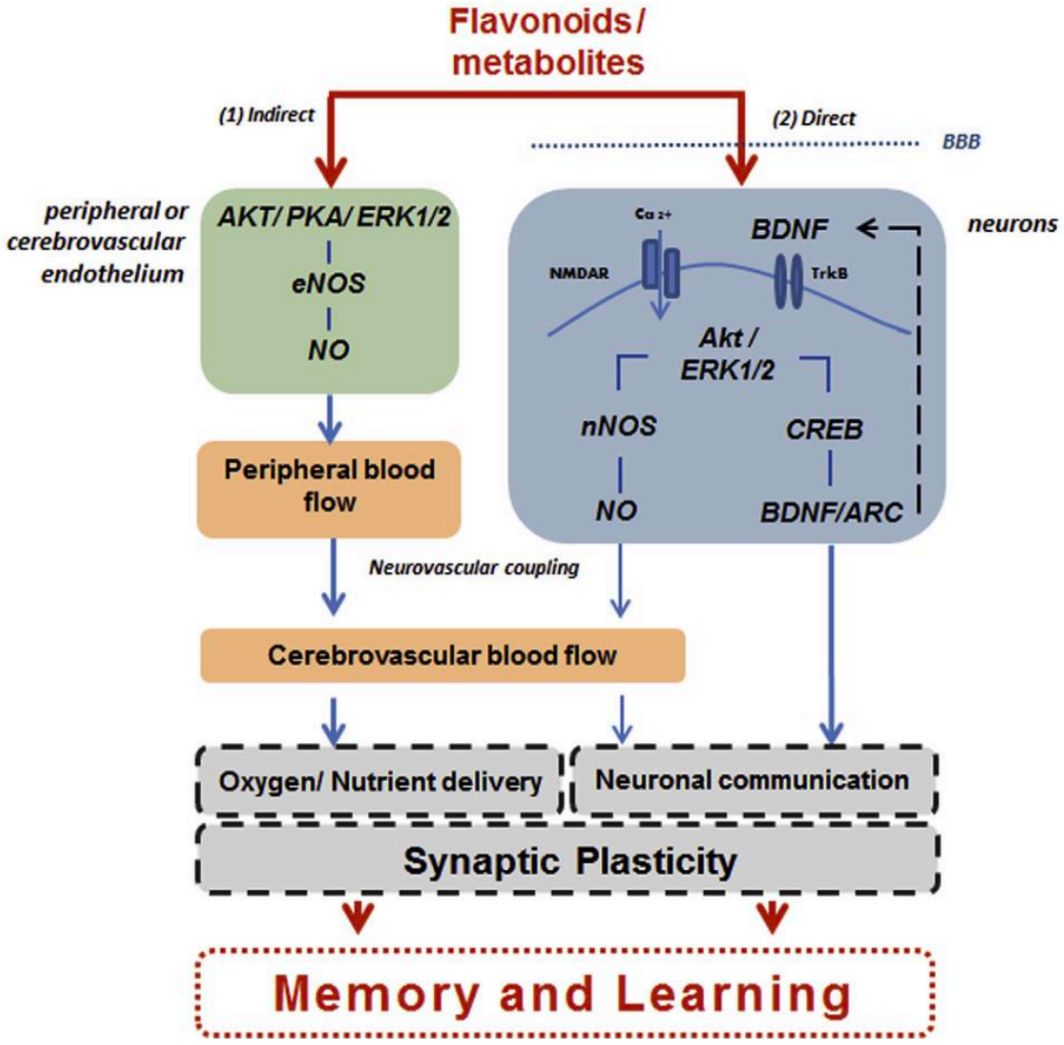



**Figure 15:** Mechanisms underlying the effective dietary flavonoids on memory and learning. Circulating flavonoid metabolites might indirectly affect brain function and cognitive performance by modulating nitric oxide dependent cerebrovascular function at the level of the cerebral endothelium crossing the Blood Brain Barrier (BBB). Some flavonoid metabolites may act centrally by modulating neuronal receptors (e.g. TrkB, NMDA), signalling kinases (Akt, ERK ½) and neurotrophins (BDNF) to changes in synaptic function. NMDAR = n-methyl-D-aspartate receptor; TrkB = Tropomyosin receptor kinase B; Akt = protein kinase B; PKA = phosphokinase A; ERK = extracellular signal-related kinase; CREB = camp responsive element binding; eNOS = endothelial nitric oxide synthase; nNOS = neuronal nitric oxide synthase; ARC = activity-related cytoskeletal protein.

Effects of the most prominent botanicals are described below:

*Curcumin:*

a) In mouse neural progenitor cells, curcumin activated extracellular signal-related kinases (ERKs) and p38 kinases, cellular signal transduction pathways known to be involved in the regulation of neuronal plasticity and stress responses. Inhibition of ERKs and p38 kinases effectively blocked the mitogenic effect of curcumin in these cells. (202)

b) In rats subjected to traumatic brain injury, dietary supplementation with a curcumin derivative counteracted a multiplicity of effects of the injury, restoring parameters of

membrane homeostasis and thus demonstrating an upregulation of neural repair and neuroplasticity. (203)

c) The cerebral arteries from aging rats as well as endothelial cells showed that curcumin promoted eNOS and AMP phosphorylation, reducing superoxide anion production and attenuating aging-related cerebrovascular dysfunction. (204)

d) Age-related loss of hippocampal synapse input specificity of long-term potentiation in mice was reversed by curcumin, re-establishing NMDA receptor dependence of induction. It also modulated hippocampal redox status by reducing age-related increases of the oxidative thiobarbituric acid-reactive substance concentration and raising depressed levels of glutathione. (205)

e) Healthy adults aged 60-85 participating in a randomised, double-blind, placebo-controlled trial showed that working memory and mood (general fatigue, change in state calmness, contentedness) were significantly improved with a curcumin supplement taken either with a single dose or over a 4-week period. (206)

*Green tea:*

a) The neurotoxicity of aluminium chloride injections into the brains of experimental rats, seen by changes in behaviour and antioxidant levels was reversed by the administration of green tea extracts. The authors suggested that the actions of (-) epigallocetachin gallate and (-) epicatechin, two compounds in abundance in green tea, improved mitochondrial and cholinergic synaptic functions. (207)

b) Cultured cells which express TrkB (a high affinity receptor for BDNF), displayed the potentiation of the neurogenic action of BDNF attributed to epigallocatechin-3-gallate (EGCG), an active ingredient of green tea. This was accomplished by binding of the green tea to the cell surface-associated 67 kDa laminin receptor. (208)

c) The mouse hippocampus displayed an enhanced response to high-frequency stimulation-evoked long-term potentiation when it was exposed to EGCG, again indicating the promotion of neuronal plasticity by this compound. (209)

d) Experimental rats administered EGCG for 26 weeks compared to controls displayed an improved reference and working memory in a radial maze, in addition to reduced plasma concentrations of lipid peroxides and enhanced plasma ferric-reducing anti-oxidation power. Lower hippocampus reactive oxygen species concentrations were also present in the EGCG-fed animals. (210)

e) The intake of catechins as a component of green tea, in addition to other polyphenols, displayed a positive association in 2,574 middle-aged adults with better language and verbal memory, but not with executive functioning, measured 13 years later. (211)

*Resveratrol:*

a) Administration of resveratrol to mice subjected to a forced swim test and tail suspension test resulted in reduced immobility times while elevating BDNF and ERK phosphorylation levels in the prefrontal cortex and hippocampus. These antidepressant activities resembled those seen with the clinical antidepressant fluoxetine. The targets thus appeared to be the hypothalamic-pituitary-adrenal axis, BDNF, and ERK phosphorylation expression in the brain region. (212)

b) A trial of rats subjected to chronic unpredictable mild stress for 5 weeks to induce depressive-like behaviour showed that resveratrol treatments for 5 weeks significantly

reversed those behaviour abnormalities (reduced sucrose preference, increased immobility time and decreased locomotor activity). At the same time the BDNF levels that had been depressed in the hippocampus and amygdala accompanied by decreased phorphorylations of ERK, cAMP, and CREB were all reversed by resveratrol, mimicking the effects of the established antidepressant drug desipramine. (213) Highly congruent results involving spatial learning memory and BDNF levels with the addition of c-fos expression in the rat hippocampus and amygdala were obtained elsewhere. (214)

c) Healthy older adults undergoing 26 weeks of resveratrol intake displayed a superior retention of words over 30 minutes compared with placebo, as well as significant increases of functional connectivity between the left posterior hippocampus and the medial prefrontal cortex as measured by fMRI. (215)

## Conclusions

Functional neurology represents an overhaul of the early concepts of the capacity of neurons to integrate and then fire, (216) followed by a period of hyperpolarisation in which neurons became resistant to further stimuli. The updated concept of functional neurology represents the neuron integrated into its environment and therefore susceptible to modulations of its signalling capacity by a vast array of external factors.

These agents of change include both electrical and chemical phenomena triggered by such external interventions as rehabilitation, manual muscle therapy, acupuncture, biofeedback, aromatherapy, yoga, cognitive exercises, eye muscle exercises, mediation, exercise, diet, and botanical nutritional supplements. A significant body of literature has shown that all these measures offer the promise of adaptability and regeneration of elements of the nervous system in specific instances, perhaps to become more generalised with the completion further research.

In terms of aging and neurodegenerative diseases in particular, healthcare practices involving modalities that could be considered to be applications of functional neurology offer the possibility of retarding (and even reversing in certain instances) the progress of these undesirable conditions.

At the very least, the research studies summarised in this communication need to be duly admitted into the pantheon of evidence-based medicine, such that their application in the doctor's office and healthcare systems in general may become more widely recognised as viable alternatives to current practices.

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*Author note*

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