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IDENTIFICATION AND CORRECTION OF ASYMMETRIC CORTICAL FUNCTION

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ABSTRACT

Considerable evidence exists to suggest that a variety if not all cortical systems can undergo some type of plastic reorganization. Modulation of afferent input (sensory deprivation or sensory increase) to the cortical areas represents at least one factor that determines the type of reorganization observed. This innate plastic response is probably determined to a certain extent by the central integrative state of the neurons and glial components of the functional projection networks involved. The central integrative state (CIS) of a neuron is the total integrated input received by the neuron at any given moment and the probability that the neuron will produce an action potential based on the state of polarization and the firing requirements of the neuron to produce an action potential at one or more of its axons. In some instances neuro-plastic responses and the resultant changes in activity lead to asymmetric functional levels in cortical projection networks. At some point of asymmetrical dysfunction a critical level of imbalance of activity or arousal levels between one cortical hemisphere and the other can result in a functional disconnect syndrome. This paper explores the processes of development and correction of neuro-plastic induced cortical asymmetry.

Keywords: Cortical asymmetry, hemisphericity, central integrative state, brain function

INTRODUCTION

Considerable evidence exists to suggest that a variety if not all cortical systems can undergo some type of plastic reorganization. Modulation of afferent input (sensory deprivation or sensory increase) to the cortical areas represents at least one factor that determines the type of reorganization observed. Sensory deprivation leads to the consequence of down regulation for connectivity and function of the target areas of the cerebral cortex. The pioneering work of Wiesel and Hubel [1, 2] involving the visual cortex has been especially well documented. Binocular visual occlusion at birth, which prevents all pattern vision, renders the majority of neurons in the visual cortex either unresponsive to light or unselective to oriented contours. The resulting situation which has developed from disuse down regulation renders the cortical system essentially dysfunctional. Increased use, on the other hand, leads to a strengthening of synaptic connections and an expansion of cortical tissue activated by the corresponding stimuli. This has been demonstrated particularly well in the somatosensory cortex,

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where increased stimulation of particular body parts results in their expanded cortical representation. This adaptive plastic response of the cortex to afferent stimulus seems to remain throughout the life of the animal [3, 4]. The overall size of the cortical surface does not seem to change, this leads to the assumption that the expansion of certain body-part representations occurs at the expense of others. Thus, while the relative size of cortical representations is determined innately by the number or density of afferent fibers from the sensory periphery, the actual size of these maps is modulated constantly as a function of sensory experience [5]. Changes in cortical map size do not necessarily mean an increase in functional performance. For instance, in the development of the visual cortex occlusion of one eye during a critical period ends up driving fewer neurons and innervating less cortical tissue than the non-occluded eye [1]. However, apart from small improvements in hyperacuity, the non-occluded eye does not seem to garner any advantage from its vastly expanded control of visual cortical neurons. It seems, therefore, that the visual cortical system is already working at some predetermined optimum, which prevents it from improving beyond its innate capability regardless of the stimulus received [5].This innate capability is probably determined to a certain extent by the central integrative state of the neurons and glial components of the functional projection networks involved. The central integrative state (CIS) of a neuron is the total integrated input received by the neuron at any given moment and the probability that the neuron will produce an action potential based on the state of polarization and the firing requirements of the neuron to produce an action potential at one or more of its axons [6,7].

In some instances the development of expanded cortical maps and the resultant changes in activity lead to asymmetric functional levels in cortical projection networks. At some point of asymmetrical dysfunction a critical level of imbalance of activity or arousal levels between one cortical hemisphere and the other can result in a functional disconnect syndrome [8, 9]. The critical level at which this functional disconnect first becomes symptomatic seems to vary between individuals. The symptomatic presentation of functional disconnection syndrome varies widely but can include conditions including attention deficit disorder and attention deficit hyperactivity disorder [10], autism [11], depression [12], asymmetric control of the autonomic nervous system, immune system dysfunction, and asymmetric modulation of sensory perception, as well as cognitive, learning, and emotional processes [12].

In this paper I discuss these concepts as well as a variety of treatment options for functional disconnection syndrome secondary to asymmetric cortical function.

ASYMMETRIC CORTICAL FUNCTION

The fact that the human brain functions in an asymmetric manner has been fairly well established in the literature [13-17]. The exact relationship between this asymmetric design and the functional control exerted by each hemisphere remains controversial.

The concept of asymmetric hemispheric function of the cortex involves the assumption that the two hemispheres of the brain control different asymmetric aspects of a diverse array of functions and that the hemispheres can function at two different levels of activation. The level at which each hemisphere functions is dependent on the central integrative state of each hemisphere, which is determined to a large extent by the afferent stimulation it receives from the periphery as well as nutrient and oxygen supply. Afferent stimulation is gated through the brainstem and thalamus, both of which are asymmetric structures themselves, and indirectly modulated by their respective ipsilateral cortices [18]. Imbalances may develop between the activation of one hemisphere and the other with a number of different etiological pathways including aberrant patterns of activation or arousal [19], acute or chronic ablative lesions [20-22], asymmetric afferentation excesses or deficits [23], inter or intra hemispheric transmission imbalances [24,25], circulation deficits, diffuse axonal injury

(concussion), asymmetric neurotransmitter concentrations [26, 27] or asymmetric metabolic dysfunction. Often a combination of these factors contributes to the state of asymmetry between the hemispheres. At some point of asymmetrical dysfunction, a critical level of imbalance of activity or arousal levels between one cortical hemisphere and the other can result in a functional disconnect syndrome [8,9]. The critical level at which this functional disconnect first becomes symptomatic seems to vary between individuals. Neuro-plastic changes may be maladaptive in cases of asymmetric cortical stimulation or inhibition resulting in a chronic state of disequilibrium in lateralized cortical systems. For example in stroke survivors ablative injury to areas of cortex may result not only in disruption of functional activities related to the site of the injury but also in a lack of inhibitory projections to the contralateral hemisphere. This sets into motion the chronic state of over excitation in the contralateral hemisphere [21, 22]. The chronic disinhibition of the contralesional cortical area may result in a vicious cycle in which the lesioned area experiences a chronic increased inhibition due to the over excitation of the contralesional site which in turn inhibits the lesioned site to even greater degree. This same cycle may develop from any of the etiologies listed above.

Asymmetries in cortical function based on fMRI, BOLD, PET and qEEG studies have been found in a number of different symptomatologies and conditions including attention deficit disorder and attention deficit hyperactivity disorder [10], autism [11] approach versus withdrawal behavior, maintenance versus interruption of ongoing activity, tonic versus phasic aspects of behavior, positive versus negative emotional valence, asymmetric control of the autonomic nervous system, and asymmetric modulation of sensory perception, as well as cognitive, learning, and emotional processes [12] and depression [28].

Hemispheric asymmetries in function have also been shown to exist under normal physiological conditions such as in the control of movement. For example, the dynamic dominance hypothesis of movement control in which the left hemisphere is proposed to have a greater contribution to dynamic control and the right hemisphere a greater contribution to positional control involved in movements of the limbs [29,30]. Blood [31] has proposed that motor and postural control exhibit opposite hemispheric dominance and may be involved with the development and maintenance of dystonias [31].

Functional hemispheric asymmetries have also been shown to exist with respect to cortical control of cardiovascular function. The research suggests that asymmetries in brain function can influence the heart through ipsilateral pathways. It is quite clear from the literature in this area that stimulation or inhibition at various levels on the right side of the neuraxis results in greater changes in heart rate, while increased sympathetic tone on the left side of the neuraxis results in a lowered ventricular fibrillation threshold. This occurs because parasympathetic mechanisms are dominant in the atria, while sympathetic mechanisms are dominant in the ventricles [32, 33].

Neurotransmitter asymmetries in the cortex have also been discovered. Quite consistent results have been reported in a number of studies that have suggested that noradrenergic innervation, the biological substrate of arousal shows a clear right hemispheric asymmetry [27, 34, 35]. Several studies have also shown strong indications that the neurotransmitter serotonin shows a right hemispheric dominance [36, 37, 38], which may occur from birth as an inborn feature of cortical function [39]. The role of gating signals, such as acetylcholine, in the enhancement of cortical plasticity [40, 41 may also play a role in the development of asymmetric activation.

Cortical asymmetries have also been documented with respect to hormonal regulation. Cortisol secretion has been associated with the right hemisphere with predominance of control demonstrated in this hemisphere during emotionally-related situations [42, 43]. Various studies have shown that right hemispheric chemical dominance was associated with up-regulation of the hypothalamic-mediated isoprenoid pathway and was more prevalent among individuals with various metabolic and immune disorders including a high body mass index, various lung diseases including asthma and chronic

bronchitis, increased levels of lipid peroxidation products, decreased free radical scavenging enzymes, inflammatory bowel disease, systemic lupus erythematosis (SLE), osteoarthritis, and spondylosis. Left hemispheric chemical dominance was associated with a down-regulated isoprenoid pathway and was more prevalent among individuals with low body mass index, osteoporosis, and bulimia.

A number of studies have indicated that cortical asymmetries may exist when different emotional states are activated. The left frontal cortex appears to be activated during the expression or experience of positive emotional states, whereas the right frontal cortex seems to be activated during the expression or experience of negative emotional states [44-47]. The severity of symptoms in depression has been linked to the activation levels in the left frontal cortex [48]. Those patients with left frontal cortex lesions with sparing of the right frontal cortex showed the most severe depressive symptoms.

Cortical asymmetry has also been shown to be important in immune regulatory functions. Natural killer cell activity was significantly increased in human females with extreme left frontal cortical activation when compared to females with extreme right cortical frontal activation [49]. The level of hemispheric activation in these women was determined by electroencephalographic (EEG) determinants of regional alpha power density. This measurement has been shown to be inversely related to emotional or cognitive brain activation [44]. A variety of animal studies have also provided direct evidence of the relationship between cerebral asymmetry and immune system function [50, 51]. Partial ablation of the left frontoparietal cortex in mice, which results functionally in relative right cortical activation, resulted in decreased immune responses and partial right cortical ablation, which would result functionally in a left cortical activation showed no change or a reduced immune response [52, 53]. Other studies have shown that the development of the lymphoid organs including the spleen and thymus occurs with left cortical lesions, whereas increased development of the spleen and thymus occurs with right cortical lesions and activation of T cells is significantly diminished in lesions involving the left cortex and elevated with lesions of the right cortex [54-56]. These findings indicate that T-cell-mediated immunity is modulated asymmetrically by both hemispheres with each hemisphere acting in opposition to the other. Increased activity of the left cortex seems to enhance the responsiveness of a variety of T-cell-dependent immune parameters, whereas increased right cortical activity seems to be immunosuppressive. B-cell activity was found not to be affected by cortical activation asymmetry [51, 57]. It appears from the findings of the above studies that changes in hemispheric activation because of either ablation of cortical areas or modulation in physiological activation levels result in changes in immunological response activity. Both hemispheres seem to be active in the modulation of immune response, with the left hemisphere enhancing cellular immune responses and the right inhibiting those responses. Some evidence does suggest that the involvement of the right hemisphere may not act directly on immune components but may modulate the activity of the left hemisphere which does act directly to regulate immune function [52].

FUNDAMENTAL FUNCTIONAL PROJECTION SYSTEMS

The cortical asymmetries outlined above become even more important clinically when we consider some of the basic fundamental functional projection systems utilized by the cortex to modulate activity in wide-ranging areas of the neuraxis. About 90% of the output axons of the cortex are involved in modulation of the neuraxis. About 10% of the cortical output axons of the cortex are involved in motor control and form the corticospinal tracts. Of the 90% output dedicated to neuraxis modulation about 10% projects bilaterally to the reticular formation of the mesencephalon (MRF) and 90% projects ipsilaterally to the reticular formation of the pons and medulla or pontomedullary reticular formation (PMRF). The cortical projections to both the MRF and the PMRF are excitatory in nature. The neurons in the MRF and some of those in the PMRF project bilaterally to excite neurons

in the intermediolateral (IML) cell columns located between T1 and L2 spinal cord levels in the grey matter of the spinal cord; however, the majority of the PMRF remain ipsilateral [58]. These neurons in the IML form the pre-synaptic output neurons of the sympathetic nervous system, and project to inhibit neurons in the sacral spinal cord regions that form the pelvic or sacral output of the parasympathetic nervous system. Following the stimulus flow through the functional system it can be seen that high cortical output results in high PMRF output, which results in strong inhibition of the IML, which in turn results in disinhibition of the sacral parasympathetic output. The bilateral excitatory output of the MRF is overshadowed by the powerful stimulus from the cortex to the PMRF (Figure 1).

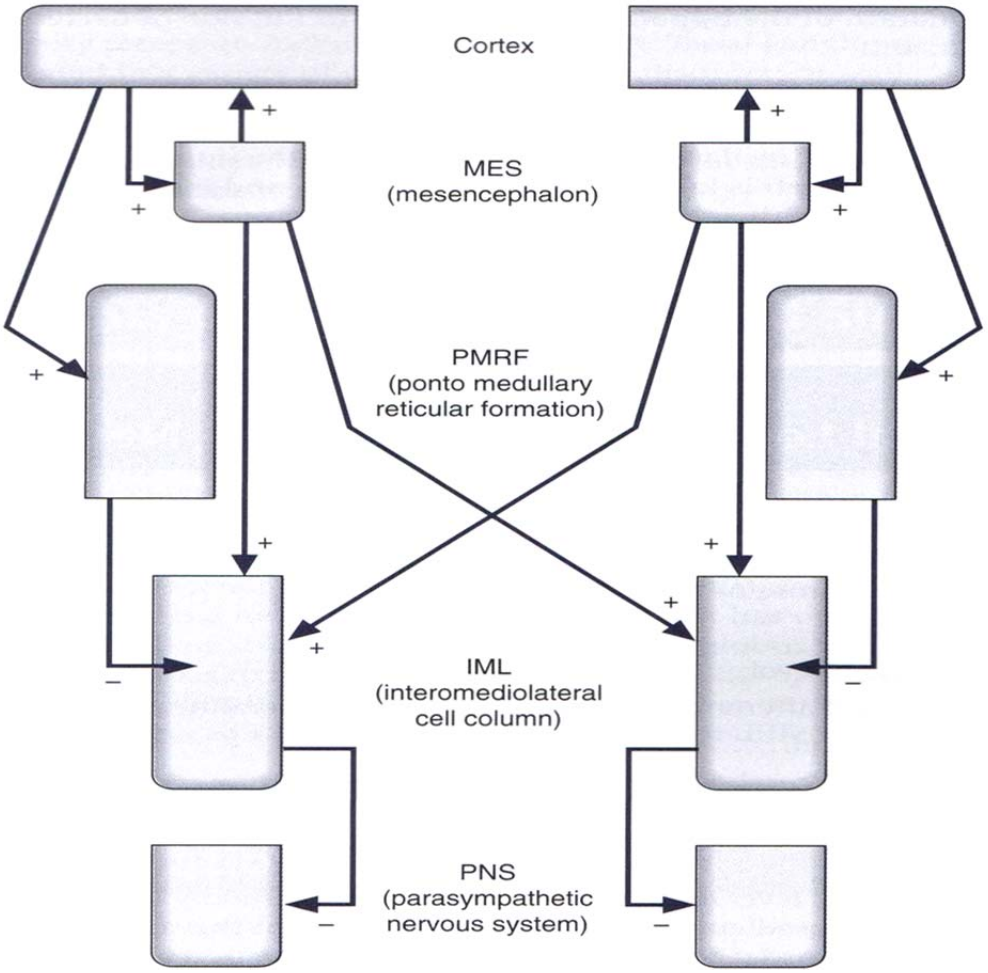

Figure 1. Functional Projection Systems from the Cortex to the Reticular Formations of the Brainstem.

To further illustrate the impact that an asymmetric cortical output could potentially have clinically, consider the affects of an asymmetric cortical output on the activity levels of the sympathetic and parasympathetic systems on each side of the body. Autonomic asymmetries are an important indicator of cortical asymmetry as this reflects on fuel delivery to the brain (sympathetic system) and the integrity of excitatory and inhibitory influences on sympathetic and parasympathetic function throughout the rest of the body. The PMRF has other modulatory effects in addition to modulation of the IML neurons.

All of the modulatory interactions of the PMRF have clinical relevance and include:

- Inhibition of pain ipsilaterally;
- Inhibition of the inhibitory interneurons which project to ventral horn cells (VHCs) ipsilaterally which acts to facilitate muscle tone—this is another example of inhibition of inhibition in the neuraxis as discussed above; and
- Inhibition of the ipsilateral anterior muscles above T6 and the posterior muscles below T6.

A sense of the clinical impact that asymmetric stimulation of the PMRF can produce symptomatically in a patient becomes apparent when it is considered that all of the following can result:

- Increased blood pressure systemically or ipsilaterally to the side of decreased PMRF stimulation, which results in differences in blood pressure between right and left sides of the body;
- Increased vein-to-artery ratio, which is most apparent on examination of the retina;
- Increased sweating globally or ipsilaterally to the side of decreased PMRF stimulation;
- Decreased skin temperature globally or ipsilaterally to the side of decreased PMRF stimulation;
- Arrhythmia if decreased left PMRF stimulation occurs or tachycardia if decreased right PMRF stimulation occurs;
- Large pupil (also due to decreased mesencephalic integration) to the side of decreased PMRF stimulation;
- Ipsilateral pain syndromes to the side of decreased PMRF stimulation;
- Global decrease in muscle tone ipsilaterally to the side of decreased PMRF stimulation;
- Flexor angulation of the upper limb ipsilaterally to the side of decreased PMRF stimulation; and
- Extensor angulation of the lower limb ipsilaterally to the side of decreased PMRF stimulation.

Clinical presentation of ipsilateral flexor angulation of the upper limb and extensor angulation of the lower limb is known as pyramidal paresis, and is an important clinical finding in many patients with asymmetric cortical function.

MEASURING CORTICAL FUNCTION

Another method used to identify cortical asymmetric activity involves the measurement of the electrophysiological activity in the cortex itself. To measure the complex patterns of brain activity tools are needed with the appropriate temporal and spatial resolution. This task is not as simple as it sounds because “appropriate resolution” varies with different types of analysis and utility expectation of the information. The measurement tool must measure the particular activity we are interested in without interfering with it to any great extent.

Neurons function through the production of two fundamentally different activities involving analogue (local field potentials) and digital (action potentials) components [59]. Both of these activities are continuously changing over time and involve multiple frequencies and amplitudes. Therefore the perfect measurement tool would be able to provide a time-frequency analysis algorithm that would provide a perfect picture of all changes in all frequencies continuously over time in

whatever spatial dimension we choose to explore. All of the current methods of measuring brain function involve a compromise between the desired temporal and spatial resolution necessary for complete analysis.

The desired temporal resolution is in the order of the operation speed of the neuron, or at very least neuron systems, which is in the millisecond arena. The desired spatial resolution varies between molecular interaction to global brain activity depending on the processes being investigated and the questions being asked. No current method exists that can continually and instantaneously monitor between decimeter and molecular spatial scales [59].

Obviously, the methods available at this time differ in their spatial and temporal resolution, and none of them achieve the highest resolution in both domains. For example what fMRI gains in spatial resolution it loses in temporal resolution and visa versa for EEG. Quantitative electroencephalography (QEEG) has been shown to be a valid instrument in the evaluation of a variety of components of cognitive function [60, 61].

Computer-assisted EEG analysis and interpretation offers multiple advantages over visual inspection of raw EEG tracings, including the ability to derive measures, perform data transforms, and identify subtle shifts in the types and patterns of EEG activity.

The most commonly used qEEG measures of these types include: frequency composition of the EEG over a given period (spectral analysis); absolute and relative amplitude (μV/cycle/second) and power (μV2/cycle/second) within a frequency range or at each channel; coherence (analogous to cross-correlation in the frequency domain between activity in two channels); phase (relationships in the timing of activity between two channels); and symmetry between homologous pairs of electrodes. Data of these types may be mapped over the scalp surface (historically referred to as brain electrical activity mapping, or BEAM, among other terms).

Statistical probability mapping of such data may be used to construct topographical maps for visual inspection. Among qEEG measures, frequency analyses and coherence are of particular interest in the study of mild TBI and post-concussive symptoms. The scalp-measured frequency of the electrical energy generated by groups of cortical neurons varies with: their numbers (i.e., as neurons are lost, the amplitude [and therefore power] of electrical energy recorded at the scalp diminishes); the integrity of the thalamocortical circuits in which they participate (i.e., injury to and/or dysfunction of those circuits results in a shift to slower frequencies recorded at scalp electrodes); and the influence of 'bottom-up' activation from the reticular system (i.e., with increases in reticular activating system activity, shifts toward higher frequencies are observed, whereas decreases in the activity of this system shifts cortical activity towards lower frequencies).

Coherence evaluates the correlation between EEG activity (in the frequency domain) between scalp electrodes, and therefore may serve as an indicator of neural network connectivity and dynamics [61]. Low resolution brain electromagnetic tomography (LORETA) [62] is another functional imaging method based on electrophysiological and neuroanatomical constraints.

LORETA and its variants have been employed by many studies seeking to analyze spectral components of EEG activation [63]. LORETA also promises to be a useful method for the localization of neural generators in the study of long-distance neural synchronization and in identifying asymmetries in cortical function (Figure 2 and 3).

The central integrative state (CIS) of a neuron is the total integrated input received by the neuron at any given moment and the probability that the neuron will produce an action potential based on the state of polarization and the firing requirements of the neuron to produce an action potential at one or more of its axons. The physical state of polarization existing in the cell at any given moment is determined by the temporal and spatial summation of all the excitatory and inhibitory stimuli it has processed at that moment. The complexity of this process can be put into perspective when you consider that a pyramidal neuron in the adult visual cortex may have up to 12,000 synaptic

connections, and certain neurons in the prefrontal cortex can have up to 80,000 different synapses firing at any given moment [64, 65].

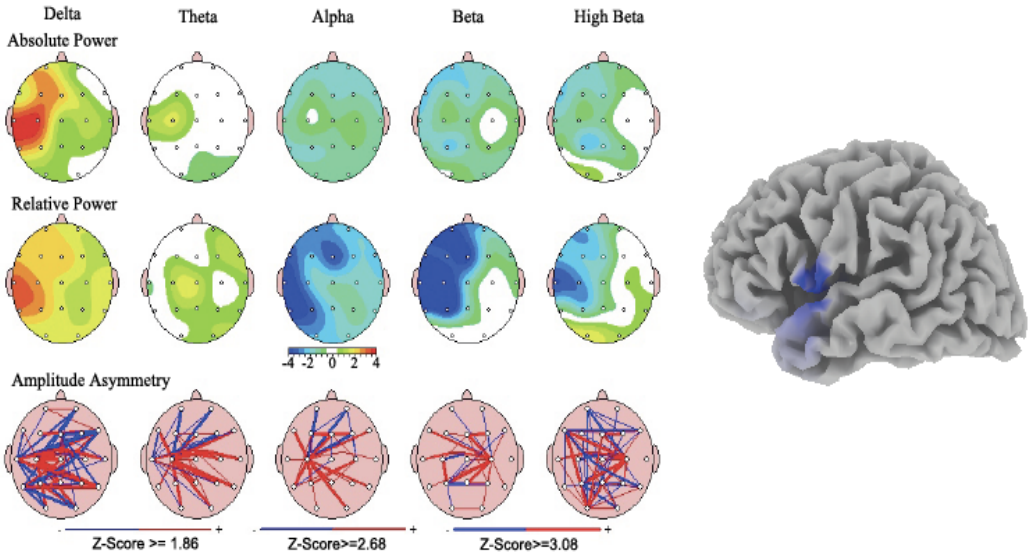

Figure 2. QEEG produced Topographic head maps and a LORETA brain image demonstrating a left hemisphere infarction in a patient.

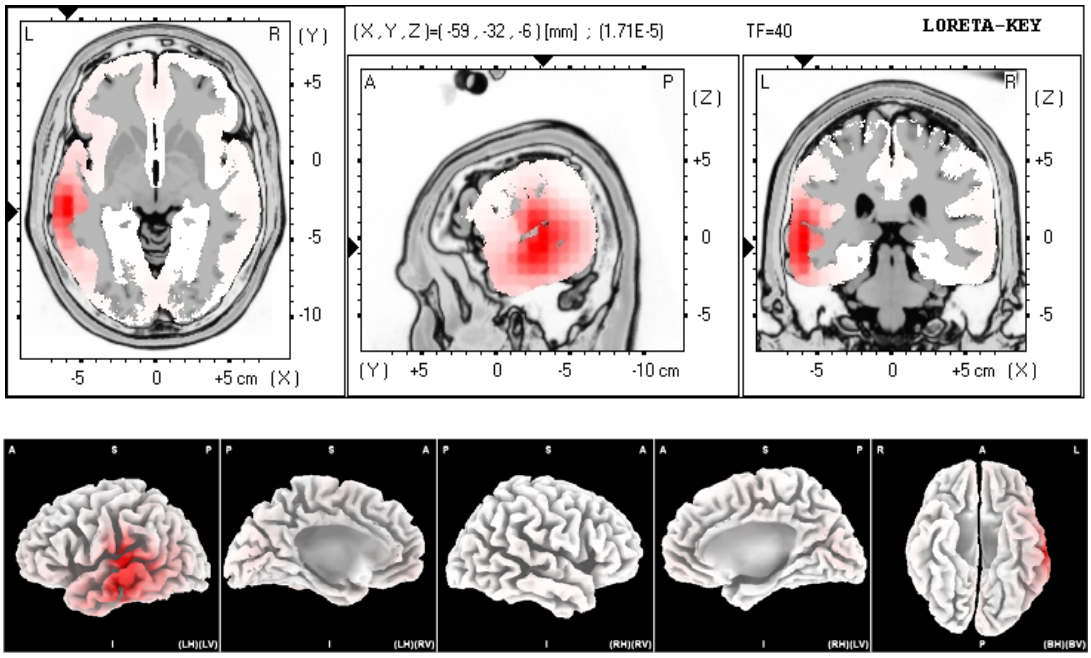

Figure 3. LORETTA images demonstrating asymmetrical cortical activation following concussion.

Treatment of Cortical Asymmetry

The treatment of cortical asymmetry centers on the understanding of neuroanatomy and the application of the concepts of central integrative state and neuro-plasticity.

Central Integrative State (CIS) of a Neuron

The firing requirements of the neuron are usually genetically determined but environmentally established and can demand the occurrence of complex arrays of stimulatory patterns before a neuron will discharge an action potential. Some examples of different stimulus patterns that exist in neurons include the 'and/or' gated neurons located in the association motor areas of cortex and the complex rebound burst patterns observed in thalamic relay cells. 'And' pattern neurons only fire an action potential if two or more specific conditions are met. 'Or' pattern neurons only fire an action potential only when one or the other specific conditions are present [66]. The thalamic relay cells exhibit complex firing patterns. They relay information to the cortex in the usual integrate and fire pattern unless they have recently undergone a period of inhibition. Following a period of inhibition stimulus, in certain circumstances, they can produce bursts of low-threshold spike action potentials referred to as post-inhibitory rebound bursts. This activity seems to be generated endogenously and may be responsible for production of a portion of the activation of the thalamocortical loop pathways thought to be detected in encephalographic recordings of cortical activity captured by electroencephalograms (EEG) [67]. The neuron may be in a state of relative depolarization, which implies the membrane potential of the cell has shifted towards the firing threshold of the neuron. This generally implies that the neuron has become more positive on the inside and the potential difference across the membrane has become smaller. Alternatively, the neuron may be in a state of relative hyperpolorization, which implies the membrane potential of the cell has moved away from the firing threshold. This implies that the inside of the cell has become more negative in relation to the outside environment and the potential difference across the membrane has become greater [68].

The membrane potential is established and maintained across the membrane of the neuron by the flux of ions; usually sodium (Na), potassium (K), and chloride (Cl) ions are the most involved although other ions such as calcium can be involved with modulation of permeability. The movement of these ions across the neuron membrane is determined by changes in the permeability or ease at which each ion can move through selective channels in the membrane. When Na ions move across the neuron membrane into the neuron, the potential across the membrane decreases or depolarizes due to the positive nature of the Na ions, which increases the relative positive charge inside the neuron compared to outside the neuron. When Cl ions move into the neuron, the neuron membrane potential becomes greater or hyperpolarizes due to the negative nature of the Cl ions, which increase the relative negative charge inside the neuron compared to outside the neuron. The same is true when K ions move out of the neuron due to the relative loss of positive charge that the K ions possess. The firing threshold of the neuron is the membrane potential that triggers the activation of specialized voltage gated channels, usually concentrated in the area of the neuron known as the axon hillock or activation zone, that allow the rapid influx of Na into the axon hillock area, resulting in the generation of an action potential in the axon [69].

The concept of the CIS described above in relation to a single neuron can be loosely extrapolated to a functional group of neurons. Thus, the central integrative state of a functional unit or group of neurons can be defined as the total integrated input received by the group of neurons at any given moment and the probability that the group of neurons will produce action potential output based on the state of polarization and the firing requirements of the group [6, 7].

The concept of the central integrative state can be used to estimate the status of a variety of variables concerning the neuron or neuron system such as the probability that any given stimulus to a neuron or neuron system will result in the activation of the neuron, or neuron system; the state of pro-

oncogene activation and protein production in the system; and the rate and duration that the system will respond to an appropriate stimulus [6, 7].

Neural Plasticity

Neural plasticity results when changes in the physiological function of the neuraxis occur in response to changes in the internal or external milieu [70]. In other words the development of synapses in the nervous system is very dependent on the activation stimulus that those synapses receive. The synapses that receive adequate stimulation will strengthen and those that do not receive adequate stimulation will weaken and eventually be eliminated. The organization of the synaptic structure in the neuraxis largely determines the stimulus patterns of the nervous system and hence the way in which the neuraxis functions. Neural plasticity refers to the way in which the nervous system can respond to external stimuli and adjust future responses based on the outcome of the previously initiated responses. In essence, the ability of the nervous system to learn is dependent on neural plasticity.

The processes of neuro-plasticity can be expressed at two interacting levels of nervous system function such as at the level of motor or sensory representations of body parts in the cortex which corresponds to representational or map plasticity; or at the neuronal level which can involve synaptic plasticity or changes in neuron activation levels or morphology [71]. In the somatosensory cortex some forms of plasticity can occur very rapidly within minutes to hours [72]. For instance, cortical neurons deafferented by peripheral nerve lesion or amputation rapidly become responsive to sensory input from adjacent functioning sites [23,73,74]. In the motor cortex neurons can also rapidly reorganize their representative maps in response to nerve lesions or ischaemic nerve block [75] or during motor practice [76-78]. It is now well documented that changes in somatocortical activation can be directly linked to both direct and indirect somatosensory input from peripheral receptors including joint receptors and muscle spindle afferent projections [79-81]. Several mechanisms have been suggested to explain these plastic changes in the cortex. These include changes in synaptic efficacy (Hebbian plasticity) or by reducing or modifying protein synthesis and proteinase activity in nerve cells via receptor activation of immediate early genes. These processes are controlled by the central integrative state of the neuron and are thus strongly influenced by the stimulation status of the neuron.

Synaptic efficacy and Unmasking of Latent Horizontal Connections

Synaptic connections are maintained by neurons when they are active and produce activity (action potentials) in the primary neurons. These connections modulate the neurons output through temporal and spatial summation characteristics at any given moment. Mechanisms responsible for this type of plasticity include long-term potentiation (LTP) and long-term depression (LTD) [82]. An intriguing example of this process has been proposed as a reason for our need to sleep and dream. The Hebbian principal of synaptic maintenance due to activation also suggests that synapses or connections between inactive neurons are being constantly degraded due to spontaneous down regulation of molecules and substrates necessary for maintenance of synaptic function. In circuits were activity levels are high these processes are refreshed by the constant activation and expression of the genes that code for the necessary substrates. Circuits that are infrequently utilized refresh their synaptic strength during sleep and dreaming [83]. During sleep the maintenance of synaptic fitness in long term memory circuits and circuits not frequently utilized while we are awake is stimulated by spontaneous slow (delta) wave oscillations and via fast wave stimulus during the REM component of sleep [84]. The activation of new and old memory circuits during REM sleep may result in what we perceive as dreams [85].

It seems that many synaptic connections that are maintained in the system have a moderate to low efficacy for individually inducing a large enough change in a neurons' membrane potential to result in

the generation of an action potential. Some of these pre-existing but semi dormant projection fibres have been referred to as horizontal fibres. Should the firing characteristics of other more primary firing inputs to the neuron change say through functional dysfunction, trauma or stroke then the effect of these synapses on the system become "unmasked" and may change their effects on the system drastically. The effects may be either beneficial or harmful to the individual depending on a complex set of circumstances including the functional area of the brain involved and the increase or decrease in inhibitory influences on the system. For example, in the case of a stroke, survivors typically experience an acute increase in perilesional excitability due to, for the most part, increases in excitatory neurotransmitters, followed by chronic changes that include changes in intracortical and interhemispheric inhibitory imbalances that manifest in a variety of physical symptoms that could facilitate or hinder recovery depending on the functional systems involved [20].

Immediate Early Gene Activation of Protein Synthesis

It is now commonly accepted that the brain controls mental, physiological and behavioural processes and that brain function is controlled by gene activation. It is also accepted that social, developmental and environmental factors can alter gene expression and that alteration in this gene expression induces change in brain function [86]. This process is accomplished by special transmission proteins called immediate early genes (IEG) which are activated by a variety of second messenger systems in the neuron in response to membrane stimulus [87,88]. Two types of IEG responses have been recognized and include Type 1 IEG responses which are specific for the genes in the nucleus of the neuron and type 2 IEG responses which are specific for mitochondrial genes [89]. These genes are activated by a complex interaction involving receptor stimulation and the biochemical status of the neuron.

Regeneration

Regeneration involves the re-sprouting or new formation of dendrites and or axons that form new synapses. This re-growth is usually associated with the release of various nerve growth factors. This type of neural plasticity can be stimulated by ablative lesions such as stroke [90].

Redirection, Reorganisation or Rerouting of Nerve Transmission

This type of plasticity includes creation of new anatomical connections (sprouting of axons and dendrites) or elimination of existing connections or by altering synapses morphologically [91]. A typical example of this type of plastic change is recovery after ischemic strokes. Mechanisms of plasticity result in re-organization of the nervous system in such a way as to allow other parts of the CNS take over some of the functions that were impaired from the ablative loss of neural tissue. For example, injury to cortical areas elicits a sequence of self-repair mechanisms, including redirection of tasks to other cortical areas. This reorganization may include functional circuits far removed from the original site of injury. This injury-induced reorganization may include enlargement of the cortical areas representative of the new circuits involved, and it may provide the neural substrate for adaptation and recovery of motor behaviour after injury [92]. This type of reorganization seems to occur spontaneously in response to injury and training can facilitate the shift of processing from damaged parts of the CNS to more functionally intact areas. Focused rehabilitation that facilitates expression of neural plasticity is presently the most effective form of reorganization stimulus but additional methods are under investigation and include stimulation of the cerebral cortex utilizing both direct current in the form of transcranial direct current stimulation (tDCS) [93,94] and magnetic currents in the form of transcranial direct magnetic stimulation (TMS) [95,96].

Apoptosis

This type of plasticity involves elimination of neurons through pre-programmed or chemically induced cell death. Most neuronal systems undergo a phase of substantial neuron death at some phase of their development. In most neuron systems about 50% of the initial neurons formed undergo cell death. This process usually occurs temporally at the same time that the axons of the system have formulated contacts with their destination areas. This suggests that a certain amount of the stimulus for neuron death may actually arise or be initiated from the axon destination field through some form of feedback system [97].The feedback mechanism may be in the form of tropic growth factors produced at the destination site tissues. Active competition by axons for these growth factors may determine which axons and thus which neurons remain alive.

Afferent Modulation of Cortical Function

The development and maintenance of functional projection systems of the neuraxis is dependant on the central integrative state of the neurons supporting the projection fibres of the system. This is dependant to a large degree on the afferent input and efferent output transmitted by the system. Changes in cortical activation can result from changes or attenuation of afferent information arriving in the cortex from peripheral or subcortical structures. The changes resulting from attenuation of the afferent input that are manifested both morphologically and functionally in the cortex seem to also occur at all levels within the projection system involved [98]. For instance, changes in cortical somatotopic maps in cats also show acute and chronic changes at the level of the spinal cord, dorsal columns and the thalamus following nerve transsection [99,100]. Similar findings have also been found in monkeys [23, 98,101].

There is extensive evidence that alterations in motor activities which involve both afferent and efferent projection systems can induce structural and functional plasticity within the cortex, basal ganglia, cerebellum and spinal cord in humans [102-105]. Novel movement performance induces changes in cortical synaptic number, strength, and topography of cortical maps in the projection systems and neural assemblies involved in the performance of the movements [106]. Peripheral sensory stimulation has also been shown to induce long lasting modulation of cortical activation and cortical motor output [107]. Cortical representation of cranial nerves has also been shown to modulate with alterations in afferent input. Hamdy, 1998, reported an increase in excitation levels in the pharynx cortical representation maps following short term (10 min) stimulation of the pharynx [108]. These changes lasted 30 minutes following the cessation of the initial stimulus. In a similar study, Ridding, 2000 showed that repetitive mixed nerve stimulation of the ulnar nerve increased the excitability of the cortical projections to the hand muscles of the same hand lasting at least 15 minutes longer than the stimulus [107]. The rapid development of these plastic changes suggests that the mechanism involves unmasking or disinhibition of pre-existing weak (horizontal) projections [71].

Approaches to Treatment of Cortical Asymmetric Function

Spinal Manipulation

Spinal manipulation of dysfunctional joints may modify transmission in neuronal circuitries not only at a spinal level as indicated by previous research but at a cortical level, and possibly also deeper brain structures such as the basal ganglia. Spinal manipulation of dysfunctional cervical joints can lead to transient cortical plastic changes, as demonstrated by attenuation of cortical somatosensory evoked responses. Cervical spine manipulation may alter cortical somatosensory processing and

sensorimotor integration [109,110]. The pathways involved in the modulation of the cortex and supraspinal structures remain controversial however Holt, Beck and Sexton have proposed the following potential mechanisms [111]:

1. Cervical manipulations excite spinoreticular pathways or collaterals of dorsal column and spinocerebellar pathways.
2. Cervical manipulations cause modulation of vestibulosympathetic pathways.
3. Cervical manipulations cause vestibulocerebellar activation of the nucleus tractus solitarius (NTS), dorsal motor nucleus of vagus, and nucleus ambiguous.
4. Manipulations may result in brain hemisphere influences causing descending excitation of the pontomedullary reticular formation (PMRF). The PMRF will exert tonic inhibitory control of the IML.
5. Lumbosacral manipulations may result in sympathetic modulation due to direct innervation of the RVLM via dorsal column nuclei or spinoreticular fibers that ascend within the ventrolateral funiculus of the cord.
6. Spinal manipulation may alter the expression of segmental somato-sympathetic reflexes by reducing small-diameter afferent input and enhancing large-diameter afferent input. This may influence sympathetic innervation of primary and secondary organs of the immune system.
7. Spinal manipulations may alter the expression of suprasegmental somato-sympathetic reflexes by reducing afferent inputs on second order ascending spinoreticular neurons. This may influence sympathetic innervation of immune system organs at a more global level.
8. Spinal manipulations may alter central integration of brainstem centres involved in descending modulation of somato-sympathetic reflexes. This may occur via spinoreticular projections or interactions between somatic and vestibular inputs in the reticular formation.
9. Spinal manipulations may alter central integration in the hypothalamus via spinoreticular and spinohypothalamic projections and the influence of spinal afferents on vestibular and midline cerebellar function.
10. Spinal manipulations may influence brain asymmetry by enhancing summation of multi-modal neurons in the CNS, monoaminergic neurons in the brainstem or basal forebrain regions, cerebral blood flow via autonomic influences, or by influencing the hypothalamic-mediated isoprenoid pathway.

CONCLUSION

It seems clear that a great deal of research has documented that the brain often works in an asymmetric fashion in order to produce accurate and efficient processing and integration of information. It also appears clear that if these asymmetric processes become unbalanced they can result in unwanted thoughts, actions and behaviors. The recognition and correction of these cortical asymmetries in clinical practice offers the great hope of reducing the afflictions experienced by humankind as a result of these dysfunctional states.

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