Functional Neurology Overview

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The human brain is a network of more than 100 billion individual nerve cells interconnected in systems that:

- construct our perceptions of the external world,
- Allow us the perception of emotions,
- Control our reactions to these perceptions
Approach to Signs and Symptoms of Disease

- Historically, the search for the cause of disorders of the nervous system has been focused on finding morphological or chemical abnormalities.
- However, symptoms and signs of many disorders of the nervous system can be caused by changes in function and not directly caused by morphological or chemical abnormalities.
It is easy to understand the focus on morphological changes rather than functional changes for diagnosis and treatment, and for describing the pathology of disorders of the nervous system. Morphological abnormalities (pathologies) are easy to visualize through current imaging techniques but it is often much more difficult to determine the cause of functional changes.
Some Conditions are Multifactorial in Nature

- There is considerable evidence that several factors contribute to the symptoms and signs of most disorders of the nervous system and, in fact, few disorders are caused by a single factor or a single event.
  
  ADHD, Depression, Headaches, Low back pain

- Some diseases only manifest themselves when several factors are present, while each factor alone will not cause noticeable signs or symptoms.
The fact that induction of neural plasticity can reverse or correct certain pathologic conditions of the nervous system means that induction of neural plasticity is a valuable addition to our arsenal of treatments.

Directing treatment towards correcting the abnormal function that causes the symptoms and signs of a disease is more beneficial to the patient, than attempts to treat their abnormal test results.
How it all Works

Environment-DNA-RNA-Protein

The proteins produced in the neuron are a result of stimulation of receptors on the cell surface from environmental stimuli. Thus, the types and amounts of protein present in the neuron at any given moment are determined by:

- the amount of oxygen and nutrients available
- the amount and type of stimulation it has most recently received.

Central Integrative State (CIS)

- The central integrative state of a neuron (CIS) 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 concept of the central integrative state can be used to estimate the status 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;
- the rate and duration that the system will respond to an appropriate stimulus.
Functional Activities that Determine CIS

The CIS of a neuron or neuron system is attenuated by three basic fundamental activities present and necessary in all neurons

1) Adequate gaseous exchange, namely oxygen and carbon dioxide exchange. This includes blood flow and anoxic and ischemic conditions that may arise from inadequate blood supply;

2) Adequate nutritional supply including glucose, and a variety of necessary cofactors and essential compounds;

3) **Adequate and appropriate stimulation** in the form of neurological communication, including both inhibition and activation of neurons via synaptic activation.

Synaptic activation of a neuron results in the stimulation and production of immediate early genes and second messengers within the neuron that stimulate DNA transcription of appropriate genes and the eventual production of necessary cellular components such as proteins and neurotransmitters.

Immediate Early Genes (IEG)

- Special transmission proteins called immediate early genes (IEG) are activated by a variety of second messenger systems in the neuron in response to membrane stimulus.
- Type 1 IEG responses are specific for the genes in the nucleus of the neuron and type 2 IEG responses are specific for mitochondrial DNA.

When you decrease appropriate stimulation to a neuron the following events may take place.

↓ CIEGr (cellular Immediate Early Gene responses).

↓ Protein production.

↓ Cellular respiration (via mitochondrial electron transport chain).

↓ ATP synthesis.

↑ Resting membrane potential (RMP).

↑ Free radical formation.

Further inhibition of cellular respiration (electron transport chain) in the mitochondria.

Transneuronal degeneration (TND) & Downstream Diaschisis
Transneural Degeneration (TND)

In situations where the neuron has not had adequate supplies of oxygen, nutrients or stimulus, the manufacturing of protein is down-regulated. This process of degeneration of function is referred to as trans-neural degeneration.
Diaschisis refers to the process of degeneration of a downstream neuronal system in response to a decrease in stimulus from an upstream neuronal system.

This reemphasizes the point that neuronal systems do not exist in isolation but are involved in highly complicated and interactive networks. Interference or disruption in one part of the network can impact other parts of the network.
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.
- The development of synapses in the nervous system is very dependant on the activation stimulus that those synapses receive.
- The synapses that receive adequate stimulation will become strengthen and the synapses that do not receive adequate stimulation will weaken and may eventually be eliminated.
Cerebral Hemispheric Asymmetry (Hemisphericity)

- The concept of hemispheric asymmetry or lateralization 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 dependant 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.
Neuron Bioenergetics

Oxidative phosphorylation
ATP production
Stage 1: Breakdown of large macromolecules to simple subunits

Stage 2: Breakdown of simple subunits to acetyl CoA accompanied by production of limited amounts of ATP and NADH

Stage 3: Complete oxidation of acetyl CoA to H₂O and CO₂ accompanied by production of large amounts of NADH and ATP
Mitochondria and ATP production
Oxidative Phosphorylation
Clinical Effects of Receptor Activation in the Brain
Electrical Synapse

- Presynaptic neuron
- Postsynaptic neuron
- Gap junction
- Cytoplasm
- Mitochondrion
- Microtubule

The gap junction is a specialized type of synapse where ions flow through gap junction channels, allowing fast communication between neurons.

Pores connecting cytoplasm of two neurons

Presynaptic cell membrane

Postsynaptic cell membrane

3.5 nm

20 nm

Ions flow through gap junction channels
Chemical Synapse
Synthesis of Small-molecule Neurotransmitters

- Occurs in presynaptic terminals
- Enzymes required for synthesis are produced in neuronal cell body
- Reach cytoplasm of presynaptic terminal by slow axonal transport (0.5 - 5mm/day)
- Neurotransmitter precursor molecules either taken into nerve terminal by specific transporters or produced locally
- Enzymes synthesise neurotransmitters
- Packaged into vesicles
Synthesis of Peptide Neurotransmitters

- Occurs in neuronal cell body
- Enzymes and propeptides packaged into vesicles in Golgi apparatus
- Reach presynaptic terminal by fast axonal transport down microtubules (up to 400mm/day)
- During transport, neurotransmitters formed by enzymatic modification of propeptides
- After exocytosis, neurotransmitters degraded by enzymes
Sequence of Events Involved in Transmission at Typical Chemical Synapse

1. Transmitter is synthesized and then stored in vesicles.
2. An action potential invades the presynaptic terminal.
3. Depolarization of presynaptic terminal causes opening of voltage-gated Ca\(^{2+}\) channels.
4. Influx of Ca\(^{2+}\) through channels.
5. Ca\(^{2+}\) causes vesicles to fuse with presynaptic membrane.
6. Transmitter is released into synaptic cleft via exocytosis.
7. Transmitter binds to receptor molecules in postsynaptic membrane.
8. Opening or closing of postsynaptic channels.
9. Postsynaptic current causes excitatory or inhibitory postsynaptic potential that changes the excitability of the postsynaptic cell.
10. Retrieval of vesicular membrane from plasma membrane.

Neuroscience, Purves et al. 3rd Edition © 2005, Sinauer Associates, Fig 5.3, p 97
Excitatory Amino Acids: Glutamate

- Excitatory neurotransmitter in >50% of brain synapses
- Non-essential amino acid that does not cross blood-brain barrier
- Synthesised from local precursors – mainly glutamine released from glial cells
- Taken up by presynaptic terminals via excitatory amino acid transporters (EATT’s) and metabolised to glutamate
- Also synthesised locally from glucose, by transamination of α-ketoglutarate derived from Kreb’s cycle
- In neurons, glutamine loaded into vesicles by vesicular glutamate transporters (VGLUT)
- After release into synaptic cleft, recycled through glial cells
Glutamate production in Neurons
Inotropi Glutamate Receptors

- 3 subtypes – names derived from agonist
- NMDA (N-methyl-D-aspartate)
- AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate)
- Kainate
PCP = phencyclidine “angel dust” (inhibits)
Related compound ketamine used as dissociative anaesthetic agent
NMDA Receptor

- N-methyl-D-Aspartate (NMDA)
- Voltage-dependent Mg\(^{2+}\) binding site
- At normal resting potentials or when cell is hyperpolarised, Mg\(^{2+}\) binds, blocking channel
- When cell is depolarised, Mg\(^{2+}\) dislodged, allowing ions to flow
- Means that NMDA receptor can be activated only when cell depolarised
Clinical Considerations:

Glutamate

- Transmitter in variety of circuits in brain involved in learning, memory and motor functions

- Probable role in chronic neuropathological conditions such as **amyotrophic lateral sclerosis** (degeneration of motor neurons in anterior horn of spinal cord, brainstem and cerebral cortex)

- Implicated in excitotoxicity: accumulation of glutamate in synaptic cleft causes excess activation of receptors, and destruction of neurons

  Important cause of neuronal damage associated with reduced blood flow (**anoxia**), resulting in increased influx of Ca\(^{2+}\) into cell (eg stroke)

- Excitotoxic action of glutamate also implicated in pathogenesis of **Alzheimer’s disease**
Inhibitory Amino Acids: 
gamma-aminobutyric acid (GABA)

- Most inhibitory synapses in brain have GABA (or glycine) as neurotransmitter
- GABA most common in local circuit interneurons and cerebellum
- Glucose is main precursor
- GABA synthesised from glutamate
GABA synthesis

GAT = GABA transporter
VIATT = vesicular inhibitory amino acid transporter

Presynaptic terminal

Glucose

Glutamate

GABA breakdown

GAT

Glutamic acid decarboxylase + pyridoxal phosphate

GABA

H$_3$N—CH$_2$—CH$_2$—CH$_2$—COO$^-$

GABA receptors

Postsynaptic cell

Glial cell
Clinical Considerations: GABA

- Inhibitory transmitter in many brain circuits (eg Purkinje cells in cerebellum)
- Alteration in GABAergic circuits implicated in many conditions (Parkinson’s disease, senile dementia and schizophrenia)
- GABA receptors thought to have a role in CNS derangement associated with hepatic failure (hepatic encephalopathy)
Biogenic Amines

- Regulate many brain functions
- Also active in peripheral nervous system
- Implicated in psychiatric disorders
- Many drugs of abuse also act on biogenic amine pathways
Biogenic Amines

L-Tyrosine (Hydroxyphenylalanine) → Tyrosine hydroxylase → L-DOPA (Dihydroxyphenylalanine) → DOPA decarboxylase → Dopamine → Dopamine beta-hydroxylase → Norepinephrine

Norepinephrine leaks out from the vesicle into the cytoplasm. Epinephrine is synthesized in the cytoplasm and then transported into the vesicle.

Epinephrine
Catecholamines: Dopamine

- Present in several regions of brain
- Degeneration of dopaminergic neurons in substantia nigra leads to motor dysfunction seen in Parkinson’s disease
- Dopamine also plays poorly understood role in some sympathetic ganglia
- Many drugs of abuse affect dopaminergic synapses in CNS
Clinical Considerations: Dopamine

- Best-know example is Parkinson’s disease
- Dopaminergic neurons in substantia nigra undergo degeneration, decreasing signals to caudate and putamen nuclei (neostriatum)
- Characterised by slow movements (hypokinetic syndrome), rigidity of extremities, and tremors (initially in hands)
- Many adult psychotic disorders, including schizophrenia, are believed to involve increased activity at dopaminergic synapses
- Cocaine and amphetamine bind to and inhibit DAT, prolonging the activity of dopamine released into the synaptic cleft – responsible for euphoric effects of cocaine
Catecholamines: Norepinephrine (= noradrenaline)

- Neurotransmitter in brainstem nucleus that projects to a number of forebrain areas that influence wakefulness, attention and feeding behaviour
- Neurotransmitter in postganglionic sympathetic nerve terminals
Noradrenergic Neurotransmission

- Dopamine converted to NE by dopamine β-hydroxylase
- Loaded into vesicles
- Cleared from synaptic cleft by NE transporter or via postsynaptic cell, where it is deaminated by MAO or α-methylated by COMT
- NE (and EPI) acts by activating α- and β-adrenergic G-protein-coupled receptors
- 2 subtypes of α-adrenergic receptors (\(\alpha_1\), \(\alpha_2\)) and 3 subtypes of β receptors (\(\beta_1\), \(\beta_2\), \(\beta_3\))
Clinical Considerations: Noradrenaline

- Role in CNS as neurotransmitter not well understood
- Believed to play role in psychiatric disorders such as depression
- Tricyclic antidepressant drugs inhibit reuptake, increasing noradrenaline levels at synapses
- Amphetamines have similar effect
Catecholamines: Epinephrine (= adrenaline)

- Present in lower amounts and in fewer brain neurons than other catecholamines
- Mainly in lateral tegmental neurons that project to hypothalamus and thalamus – function not known
- Synthesised by phenylethanolamine-N-methyltransferase (present only in EPI-secreting neurones) – otherwise similar to norEPI
- EPI acts on both α- and β-adrenergic receptors
Indoleamine: Serotonin (5-Hydroxytryptamine)

- Initially thought to increase vascular tone by virtue of its presence in serum – hence name *serotonin*
- 5-HT synthesised from tryptophan, which is taken up by plasma membrane transporter
- Synthesis involves 2-step process
Serotonin (5-HT)

- Primarily in neurons of pons and upper brainstem
- Widespread projections to forebrain and cerebellum
- Forebrain projections regulate sleep and wakefulness
Clinical Considerations:

Serotonin

- Important role in mental depression
- Has lead to extensive use of SSRI’s as antidepressants
- Increase serotonin levels in brain
- Best-known example is fluoxetine hydrochloride “Prozac”
- 5-HT receptors also site of action of drugs of abuse, such as “Ecstasy” (3,4-methylenedioxymethamphetamine – MDMA)
- Cognitive defects, memory defects and undesirable psychiatric side effects associated MDMA use believed to be caused by degeneration of serotonin-containing neurons
Neuropeptides

- In excess of 100 pharmacology active neuropeptides implicated as neurotransmitters
- Some involved in modulating emotions
- Others (substance P and opioids) involved in perception of pain
- Still others (melanocyte-stimulating hormone, adrenocorticotropic hormone, and β-endorphin) regulate complex responses to stress
Neuropeptide Transmitters:

1. Brain/gut peptides
   *eg, substance P*

2. Opioid peptides
   *eg, enkephalins, endorphins and dynorphins*

3. Pituitary peptides
   *eg, vasopressin (ADH), oxytocin, adrenocorticotropic hormone (ACTH)*

4. Hypothalamic-releasing hormones
   *eg, thyropropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH)*

5. Miscellaneous
   *eg, angiotensin II*
Potent hypotensive agent

Discovered by accident, as unidentified component of powder extracts from brain and intestine

In humans, high concentrations in hippocampus, neocortex and in GIT

Released from C fibres in peripheral nerves (convey afferent pain and temperature signals)

Neurotransmitter in spinal cord, where release can be inhibited by opioid peptides released from interneurons – important mechanism of pain suppression
Opioid Peptides

- Endogenous compounds that mimic actions of morphine
- Effects mediated by metabotropic peptide receptors
- Activate receptors at very low concentrations
- In general, tend to have depressant activity (analgesics)
- 3 classes: endorphins, enkephalins, and dynorphins
- Widely distributed throughout brain, but high concentrations in periaqueductal gray matter (important part of the descending pathways that regulate pain signals)
- Enkephalins and dynorphins also in regions of spinal cord involved in modulation of pain