Neuroplasticity and Neuropsychiatric Disorders

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Recognitions and Conflict Statement

Recognition of Contribution

- Marom Bikson
- Felipe Fregni
- Michael A. Nitsche
- Robert Thatcher
- Walter Paulus
- Alvaro Pascual-Leone
- Steven C. Cramer

Conflicts

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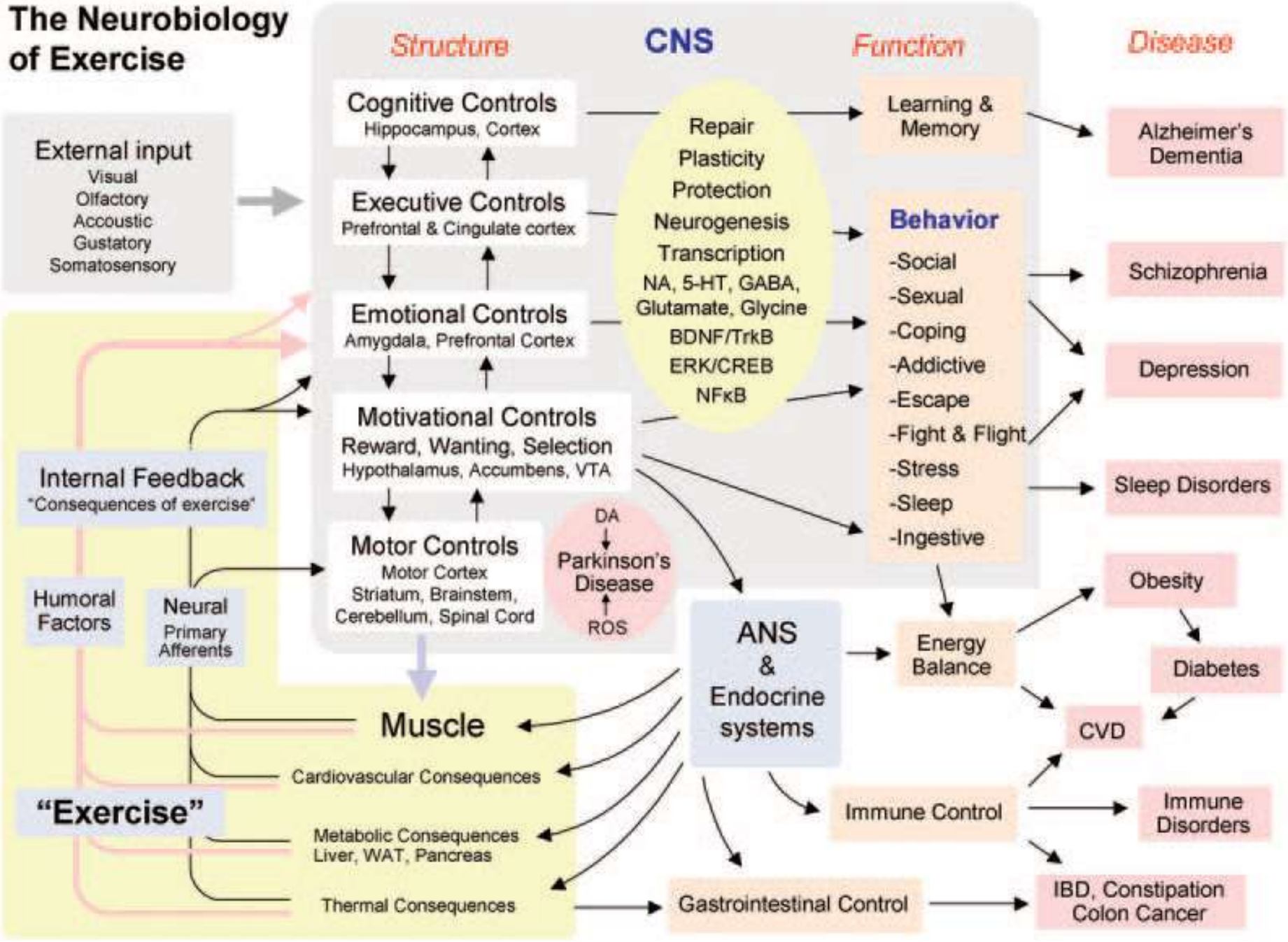
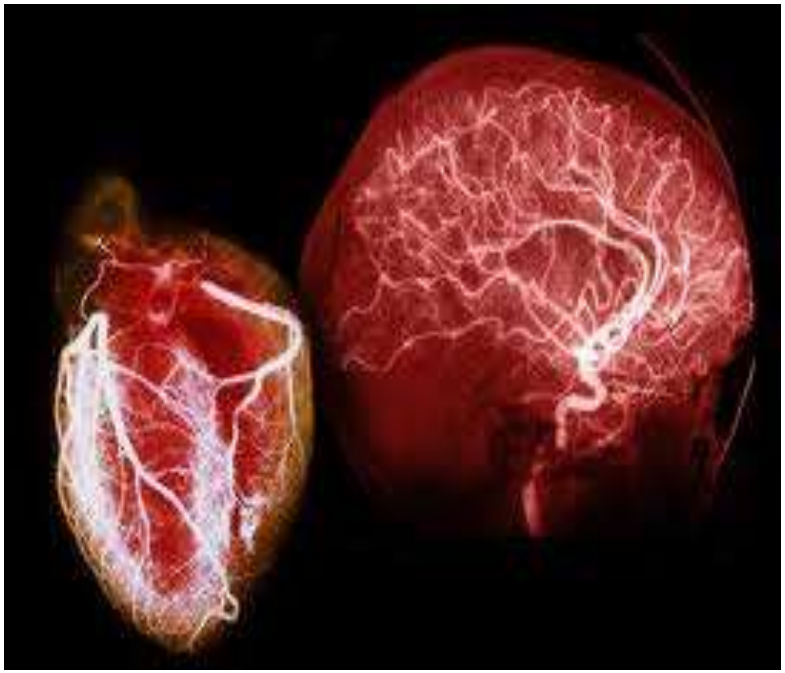


From **Dishman** etal. Obestity Vol. 14 No. 3 March 2006:345-356.

Functional Activities that Determine Neuron Health

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

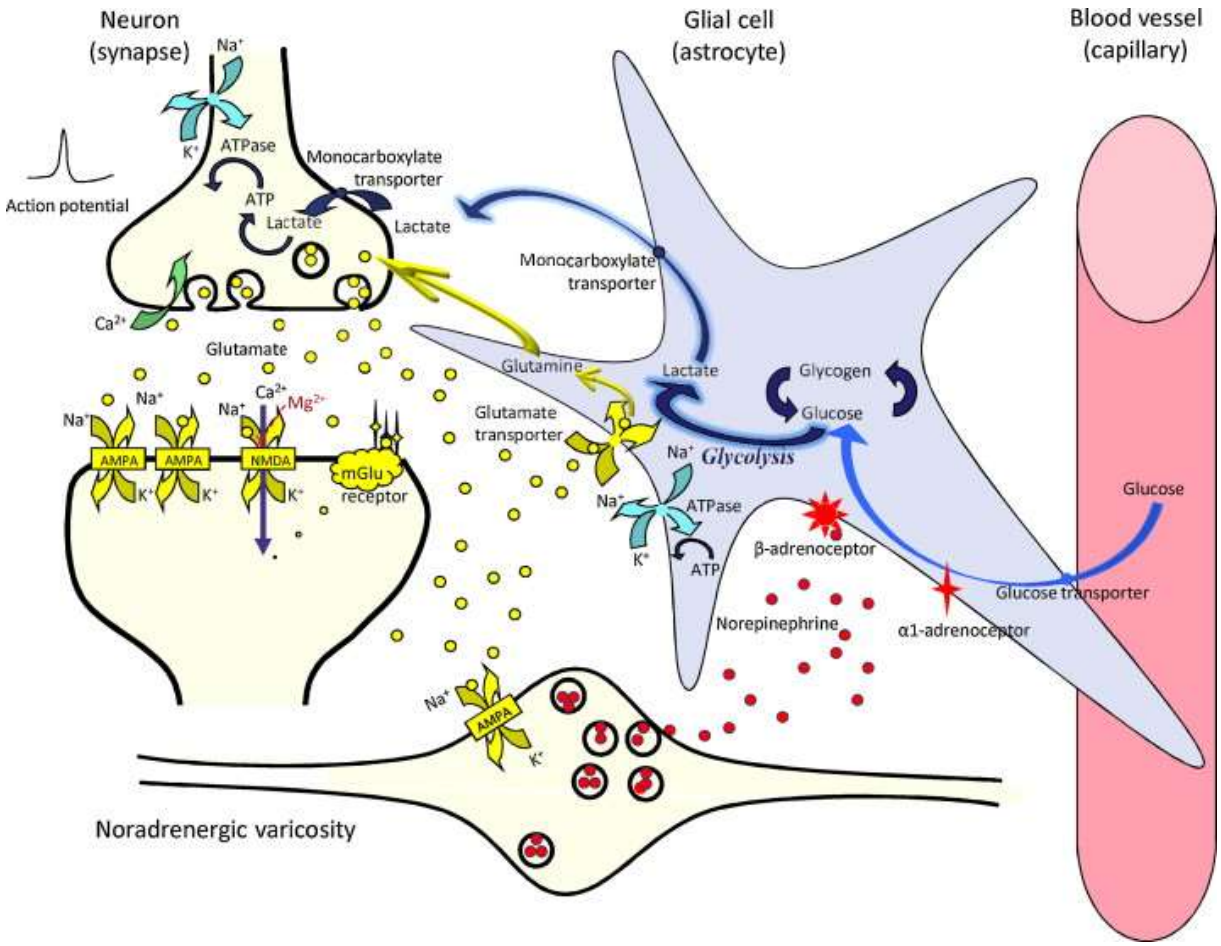


1) Adequate gaseous exchange, namely **oxygen** and carbon dioxide exchange. This includes blood flow and anoxic and ischemic conditions that may arise from inadequate blood supply

Beck R.W. Functional Neurology for Practitioners of Manual Medicine. Elsevier 2012.

Adequate and Appropriate Nutritional Supply

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



Adequate and Appropriate Stimulation

3) Adequate and appropriate **stimulation**

In the form of neurological communication including both **inhibition** and **excitation** of neurons via synaptic activation

Beck R.W. Functional Neurology for Practitioners of Manual Medicine. Elsevier 2012.

Neuronal Plasticity

Neuroplasticity can be broadly defined as the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function and connections.

It can be described at many levels

- Molecular
- Cellular
- Systems
- Behavior

- and can occur during development, in response to the environment, in support of learning, in response to disease, or in relation to therapy.

Cramer, S etal. Brain 2011: 134; 1591–1609

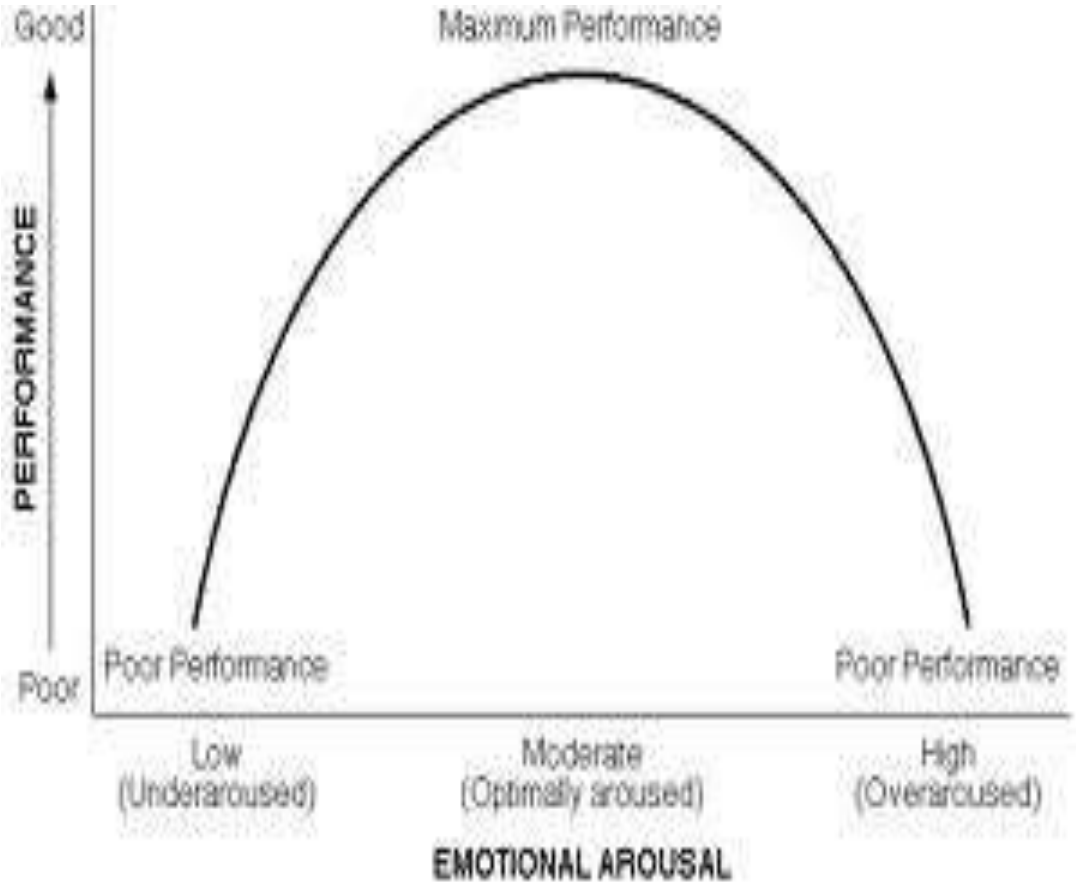
Neuroplasticity: Good or Bad?

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

Such plasticity can be viewed as adaptive when associated with a gain in function or as maladaptive when associated with negative consequences such as loss of function or increased injury, points illustrated by animal models and some human studies
(Nudo, 2006)

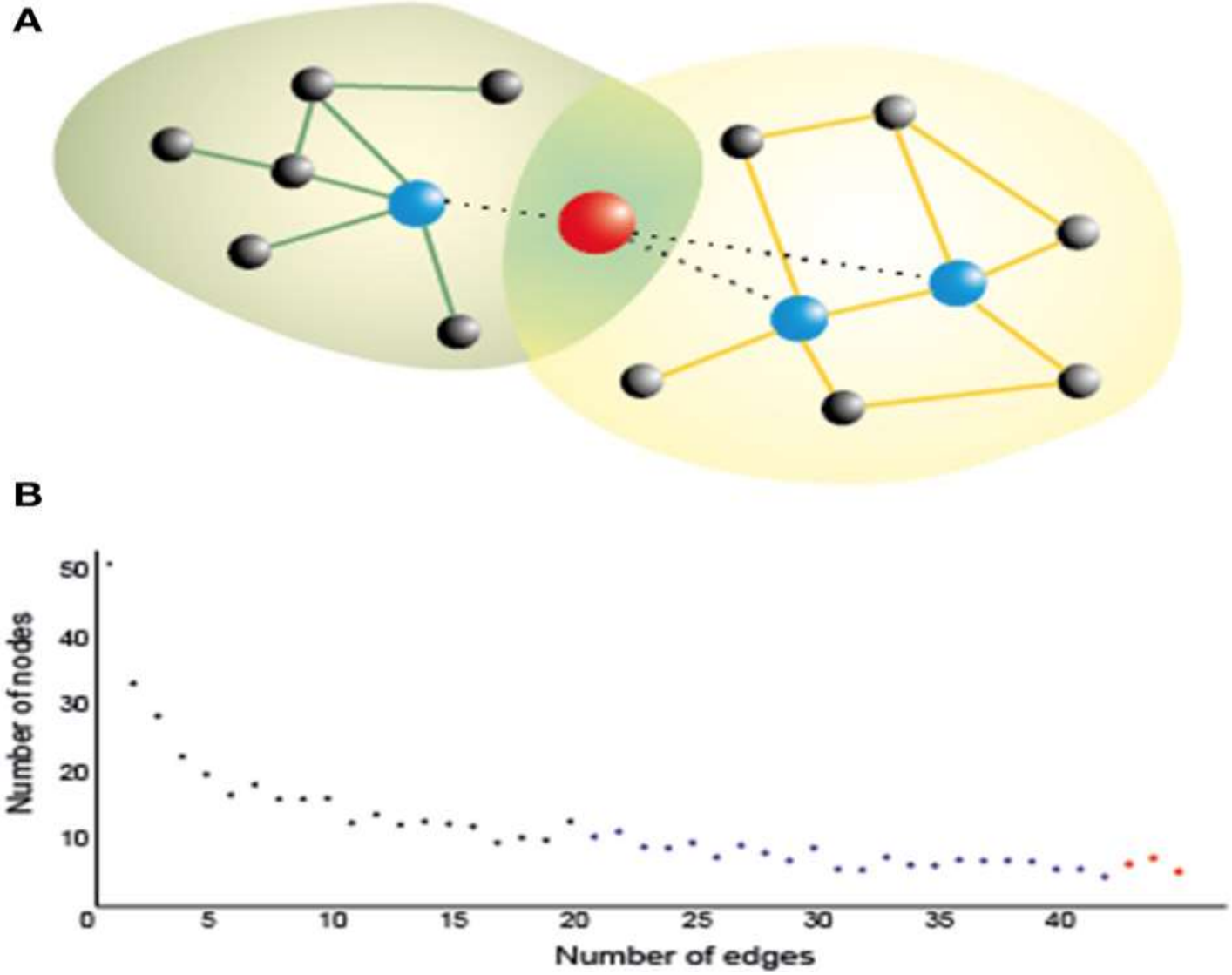
Cognitive Performance

- Peak cognitive function is near the top of the inverted ‘U’,
- Reduced coherence (hypocoherence) or hypoactivation is related to reduced functional connectivity (i.e., disconnection syndrome)
- Increased coherence or hyperactivation (hypercoherence) is related to reduced functional differentiation.



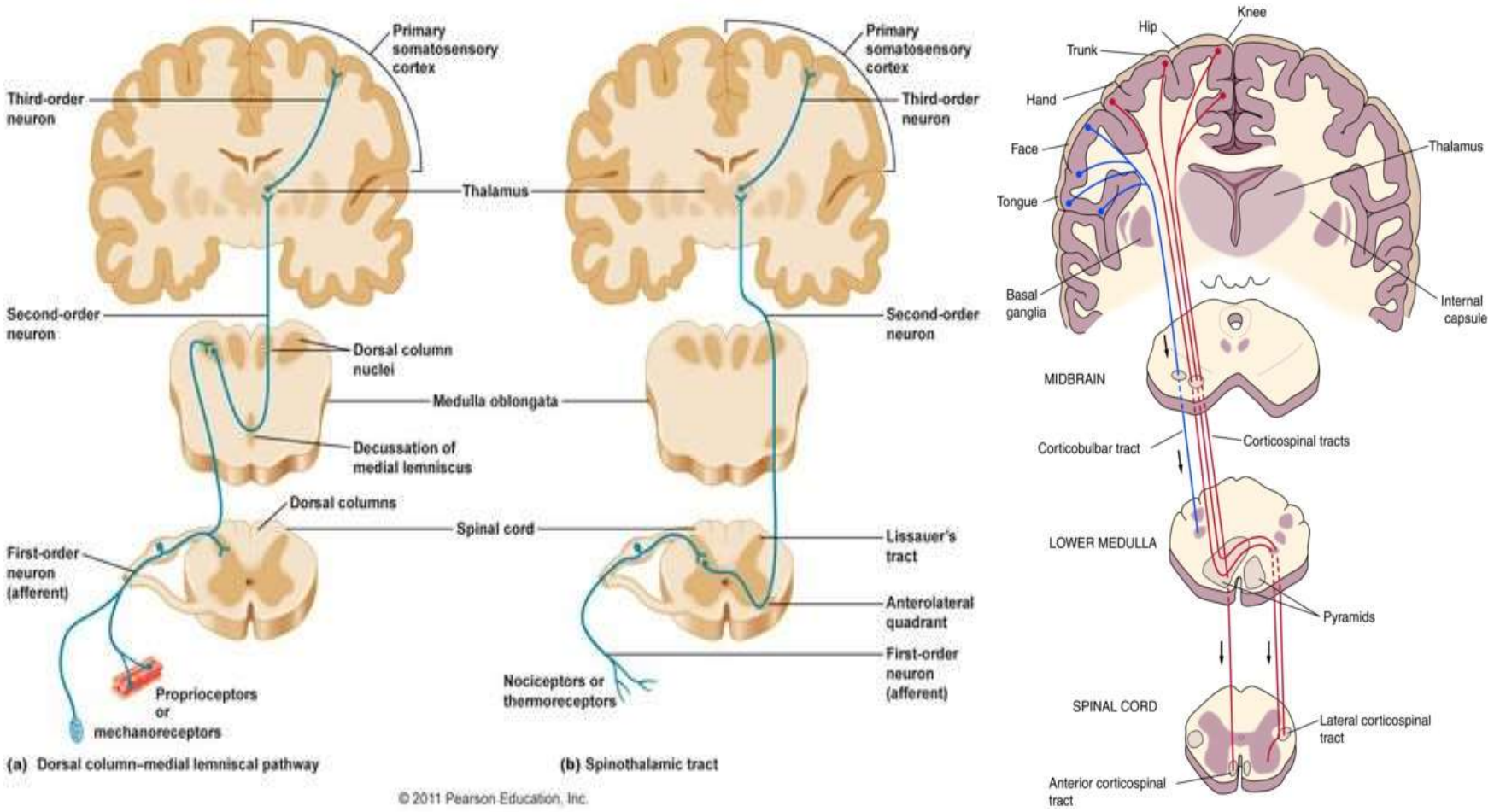
Yerkes–Dodson Law

All therapies need to consider the network activity and connective hubs between networks

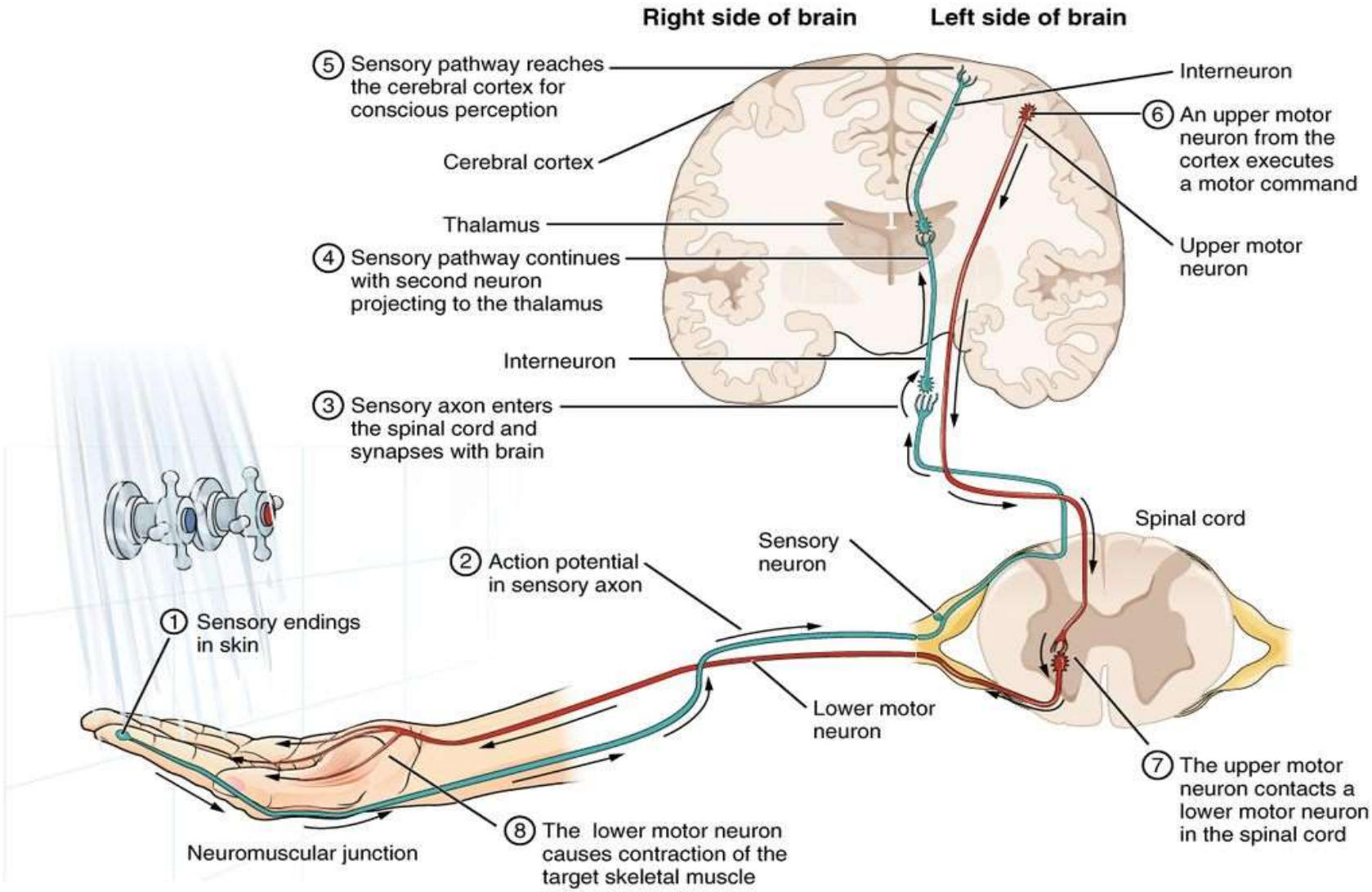


Overview of Peripheral Stimulation Pathways

Peripheral stimulation



Activity in peripheral receptors changes activity in cortical areas.
Modifying and regulating this input can modulate the activity in projection areas of the cortex



Specific Stimuli can be directed into specific cortical areas modulating activity

Case Studies: Clinical Protocols

- Shankar R, Boland C . Jalihal V., Oak K. Organ C, Beck RW, Laugharne R, Woldman W, McLean B. **EEG markers in people with Emotionally Unstable Personality Disorder and role of neurofeedback - A systematic review** Submitted to Nature Reviews Neuroscience, 2018

- Beck RW**,** Laugharne J, Laugharne R, Woldman W, McLean B, MT Beck, Mastropasqua C, Jorge R, Shankar R**. Modulating cortical asymmetry: The transdiagnostic reduction of depressive and anxiety symptoms uitlising a novel treatment approach.** The proceedings of the International Society for Developmental Neuroscience, Japan, 2018.

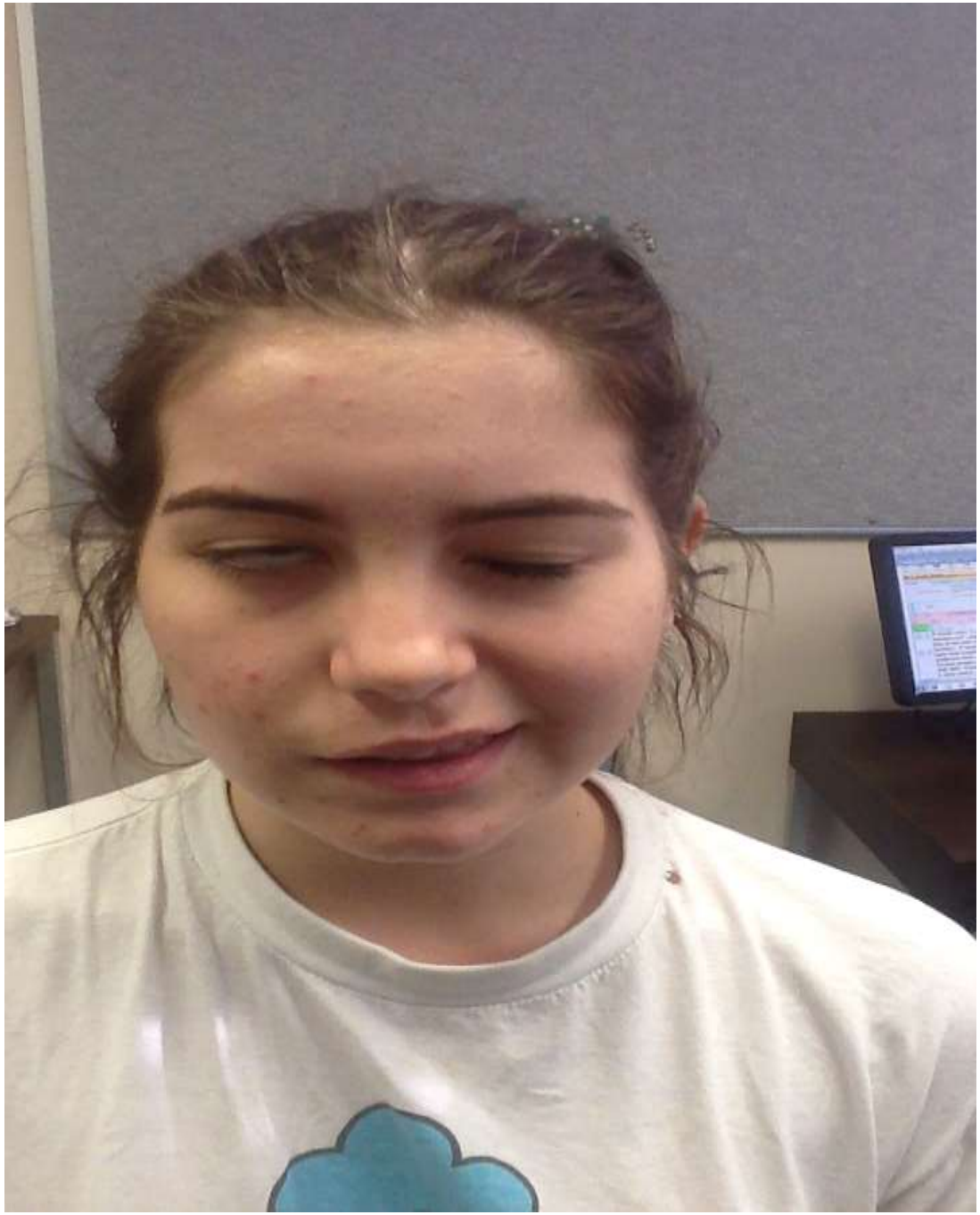
- Beck RW**,** Laugharne J, Laugharne R, Woldman W, McLean B, Mastropasqua C, Jorge R, Shankar R. **Abnormal cortical asymmetry as a target for neuromodulation in neuropsychiatric disorders: A narrative review and concept proposal**. Neuroscience and Biobehavioral Reviews 83 (2017) 21–31

- Beck RW**. Identifying and Treating Cortical Asymmetry with EEG and LORETA Imaging**. Journal of Functional Neurology and Rehabilitation. Vol1:1, 2013

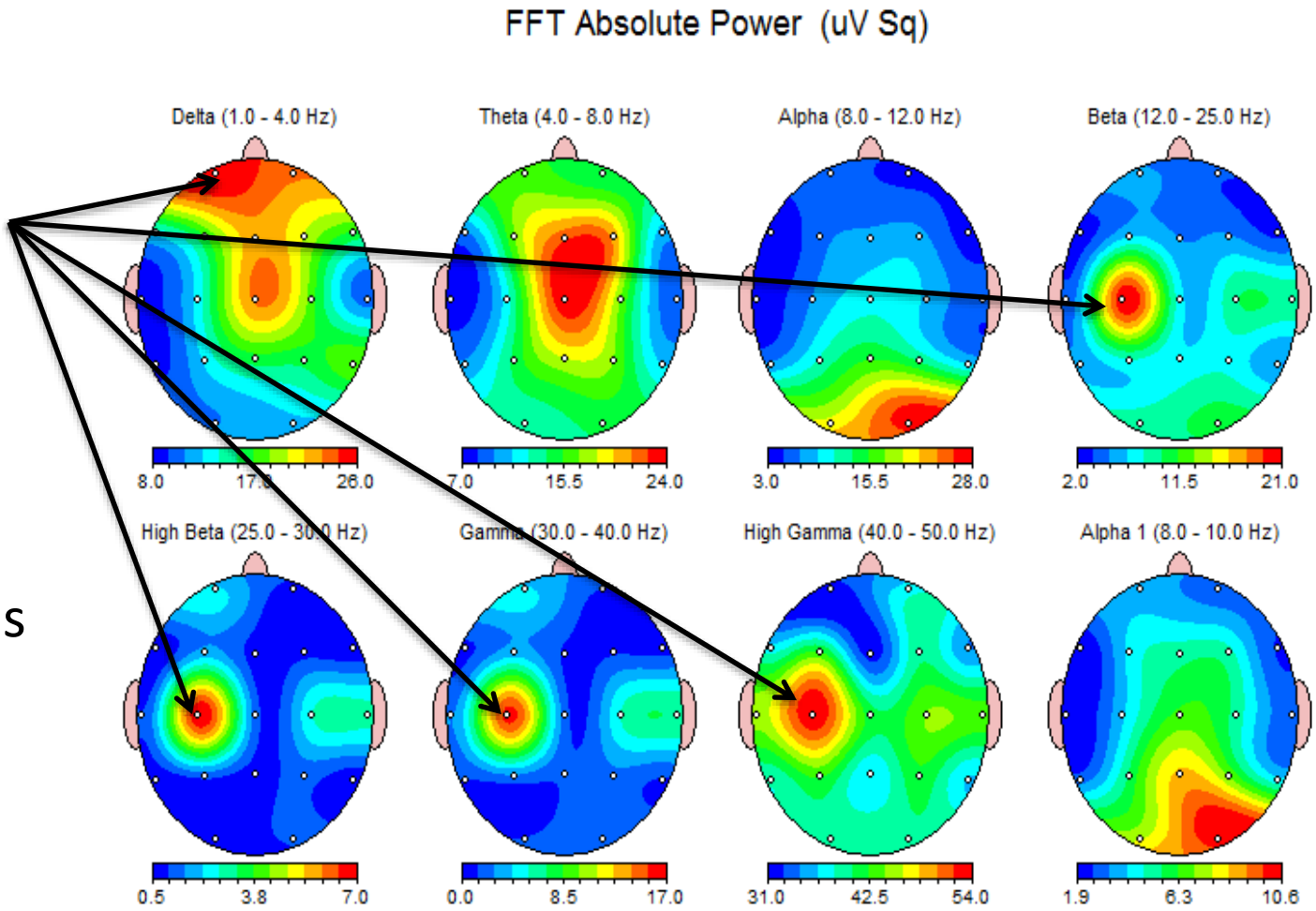
- Beck, RW. **Direct Current Stimulation Guided by EEG and LORETTA Imaging and Post-scar epilepsy**. Advances in Functional Medicine Vol.1:1 2013.

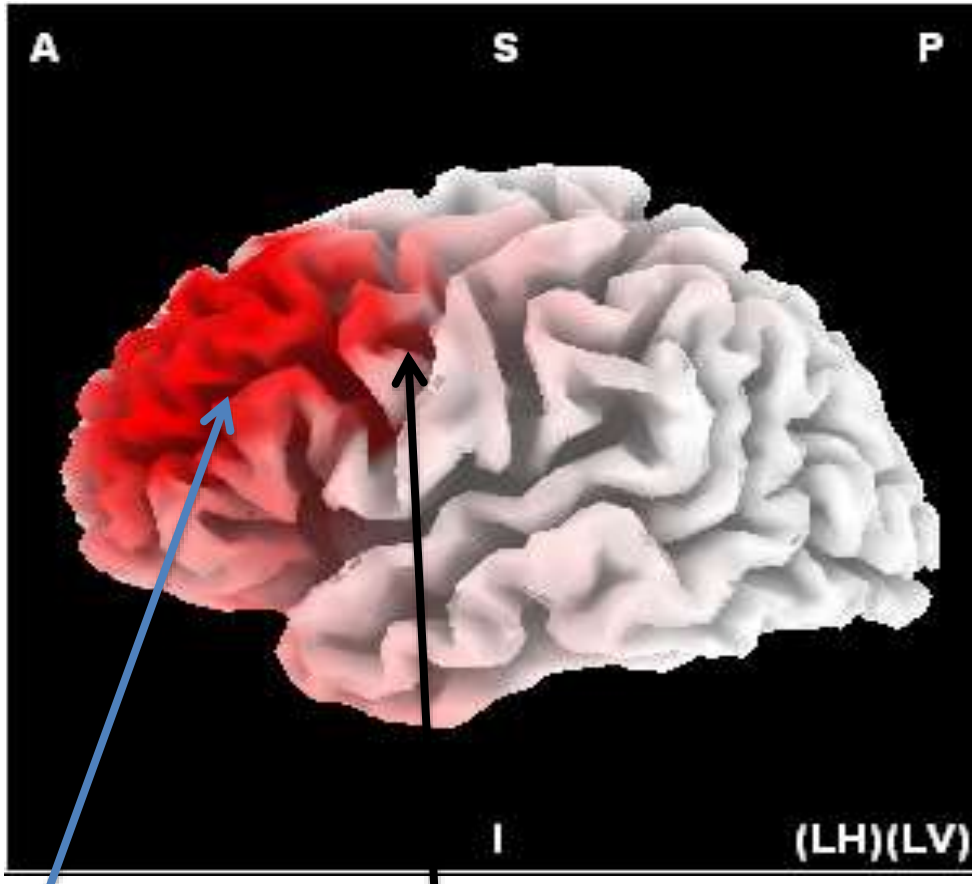
Therapy Case Study

- EEG/LORETA targeted Peripheral Stimulation
- Nutritional Supplementation
- Home Stimulation Program



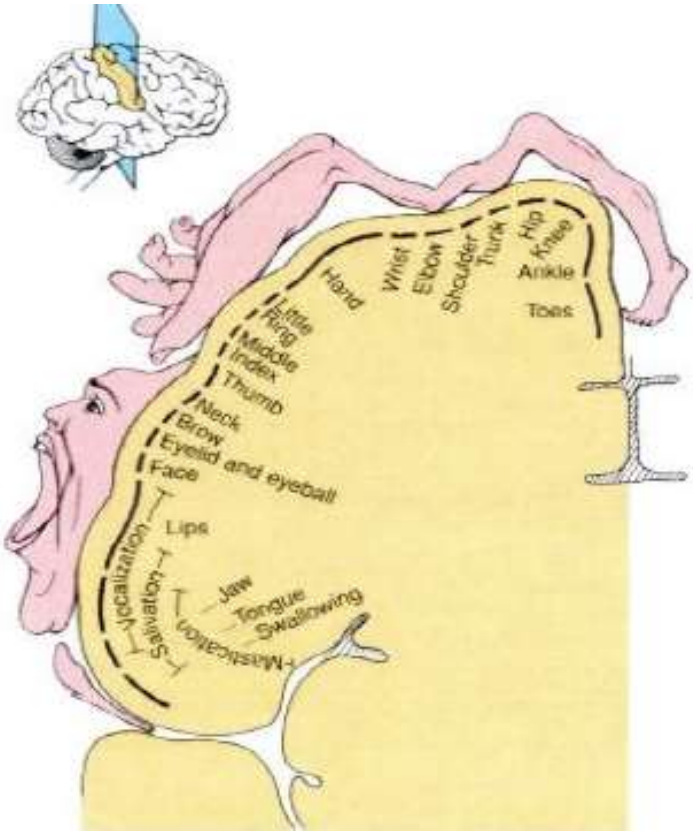
Hyper-activation in frontal cortex including frontal eye fields and facial upper motor neurons





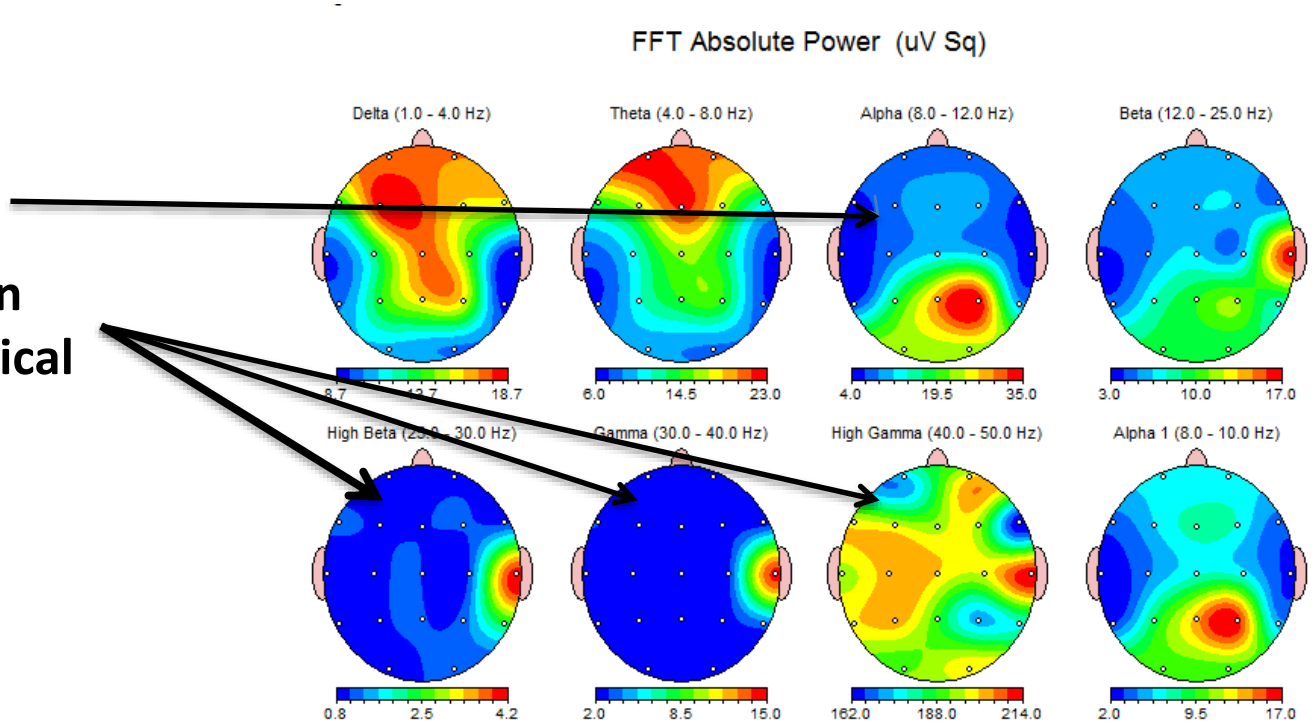
Frontal eye field

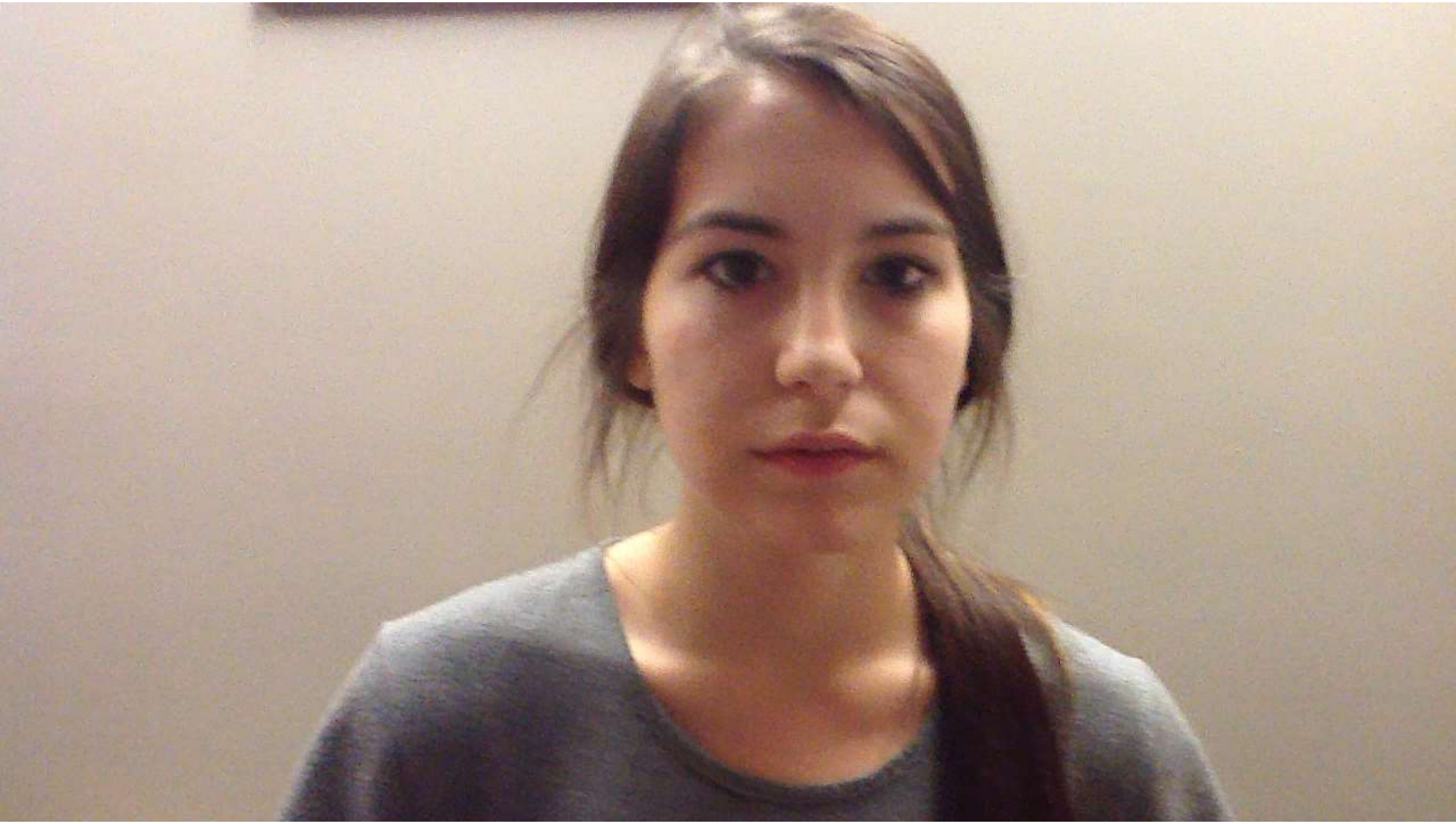
Facial Upper motor neurons



QEEG 6 weeks later

Areas of hyper-activation in frontal cortical areas have resolved





Neurofeedback

Borderline Personality Disorder

Neurofeedback

- The clinical treatment aspect of qEEG is represented by the science of EEG Biofeedback also called Neurofeedback (NF).
- NF clinical treatment is based on the use of a reinforcement and operant conditioning to train patients to modify specific EEG frequencies and phases at particular scalp locations, including the use of 3-dimensional source analysis to modify the EEG generated in specific brain regions such as the anterior cingulate gyrus or lateral pre-frontal lobes, etc.

What is Borderline Personality Disorder?

- One of ten personality disorders
- Frequently encountered in psychiatric practice
- Complex disorder characterized by pervasive instability of interpersonal relationships, self-image and mood and impulsive behaviour
- There is a pattern of rapid fluctuation from periods of confidence to despair, with fear of abandonment and chronic feelings of emptiness
- Transient psychotic symptoms including brief delusions and hallucinations may also be present

"People with BPD are like people with third degree burns over 90% of their bodies. Lacking emotional skin, they feel agony at the slightest touch or movement."
Marsha M. Linehan

"My skin is so thin that the innocent words of others burn holes right through me."

Why is understanding BPD important?

- Suicidal thinking and self harm
- High risk of suicide with 60 to 70% attempting suicide
- Completed suicide approximately 10%
- Significant financial cost to the healthcare system, social services and wider society
- Variability of response to treatment – generally poor
- Polymorphic disorder

"The Queen is controlling, the Witch is sadistic, the Hermit is fearful, and the Waif is helpless." Each requires a different approach

Christine Ann Lawson
Understanding the Borderline

Relationship of EEGs in mental health psychopathology

Only review papers in the last 20 years included

Paper	Findings
Hughes et al, 1999	-EEG and Quantitative EEG changes can be seen in anxiety disorder, depression, dementia, obsessive-compulsive disorder, schizophrenia, learning disabilities and ADHD
Shelley et al, 2009	Higher incidence of EEG abnormalities in the nonepileptic neuropsychiatric population
Balogh et al, 2010	-Patients with a diagnosis of schizophrenia, anorexia nervosa or BPD exhibited a decrease in amplitude & those with depression and anxiety an increase in amplitude of error-negativity (an evoked potential component)
McLoughlin et al, 2013	-EEG has improved understanding of face processing, cognitive control and mirror neuron activity in the general population. - Independent component analysis of EEG can identify brain sources that correspond to distinct suggested emotions
Schoenberg et al, 2014	-81% of articles reported clinical amelioration related to biofeedback, 65% to a statistically significant level ($p<0.05$) -EEG neurofeedback was the most investigated modality of biofeedback -Anxiety disorders were the most commonly treated with biofeedback -Multi-modal biofeedback appeared most effective in significantly ameliorating symptoms
Gallinat et al, 2016	-Specific EEG changes in Alzheimers disease (increase in delta and theta activity, decrease in beta activity, slowing of the basic rhythm and reduction of the topographical structure) -EEG changes in delirium (slowing of delta and theta activity) - EEG changes specific to Lithium intoxication, Clozapine and Benzodiazepines

Neurofeedback and BPD

- Amygdala neurofeedback via fMRI associated with successful down-regulation of right dorsal amygdala activation

- Reduced dissociative experiences and improvements in emotional regulation after neurofeedback training

- Such results demonstrate that neurofeedback may improve brain connectivity and emotional regulation

"You are a warrior in a dark forest, with no compass and are unable to tell who the actual enemy is, So you never feel safe .." **Anonymous**

Can EEG changes be a bellwether for neurofeedback in BPD?

- Predetermination by expert group of five criteria
- PRISMA guidance followed to conduct:
- 1) Online database search using Medline, Psychinfo and Embase
- 2) Search for grey literature
- 3) Review of the references of articles meeting three or more criteria
- 4) Search of particularly relevant articles meeting three or more criteria for “cited by” references in PubMed, Scopus and Google Scholar
- 5) Contacted authors of relevant articles about any unpublished articles/ results
- There were no language limits in the search strategy, provided there was an English language translation of the relevant study available
- The search were carried out by 2 researchers and independently verified by a 3rd

Search terms:

(“eupd” OR “borderline disorder” OR “borderline patient” OR “borderline condition” OR “borderline client” OR "borderline personality" OR "borderline personalities” OR “bpd” OR “borderline state” OR “affective instability” OR "personality disorder" OR "personality disorders” OR "PERSONALITY DISORDERS" OR "ANTISOCIAL PERSONALITY DISORDER" OR "BORDERLINE PERSONALITY DISORDER” OR “antisocial personalities" OR "antisocial personality” OR “anti-social personalities" OR "anti-social personality” OR “sociopath” OR “psychopath” OR “psychoneurotic” OR “psychoneuros*” OR “impulsivity” OR “impulse control” OR “multi-impulsivity OR multi-impulsive” OR “character disorder” OR “impulsive behaviour" OR "impulsive behavior” OR "IMPULSIVE BEHAVIOR” OR "DISRUPTIVE, IMPULSE CONTROL, AND CONDUCT DISORDERS” OR “post traumatic” OR “posttraumatic” OR “ptsd” OR "STRESS DISORDERS, POST-TRAUMATIC” OR “dyssocial” OR “socio-path”)

AND
(“ AROUSAL” OR “arousal” OR “arouse” OR “aroused” OR “vigilance” OR “rest state" OR "resting state” OR “rest states” OR “resting states” OR "acute phase” OR “abnormal” OR “abnormality “ OR “abnormalities” OR “crisis” OR “crises” OR “distress” OR “distressed” OR “agitated” OR “agitation” OR "PSYCHOMOTOR AGITATION” OR “panic” OR “PANIC” OR “depressed” OR “depression” OR “depressive” OR “DEPRESSION”)

AND
(“eeg” OR “electroencephalogram” OR “electroencephalograms” OR “electrograph*” OR “electrograms” OR “electrogram” OR “electroencephalograph” OR “ ELECTROENCEPHALOGRAPHY” OR "BRAIN WAVES” OR “ TELEMETRY” OR “telemetry” OR “ptsw” OR “slow wave" OR "slow waves” OR “p300” OR "EVENT-RELATED POTENTIALS” OR “P300” OR “EVOKED POTENTIALS” OR "CONTINGENT NEGATIVE VARIATION” OR “EVENT-RELATED POTENTIALS” OR “orbito-frontal” OR “orbitofrontal” OR “qeeg” OR “p3a” OR p3b” OR “evoked potential*” OR “event related potential*” OR “Bereitschaftspotential” OR "readiness potential” OR “cnv” OR "contingent negative variation”” OR “brain wave*” OR “alpha wave*” OR “beta wave*” OR “delta wave*” OR “gamma wave*” OR “theta wave*” OR “alpha rhythm*” OR “beta rhythm*” OR “delta rhythm*” OR “gamma rhythm*” OR “rhythm wave*”)

Criteria & Results

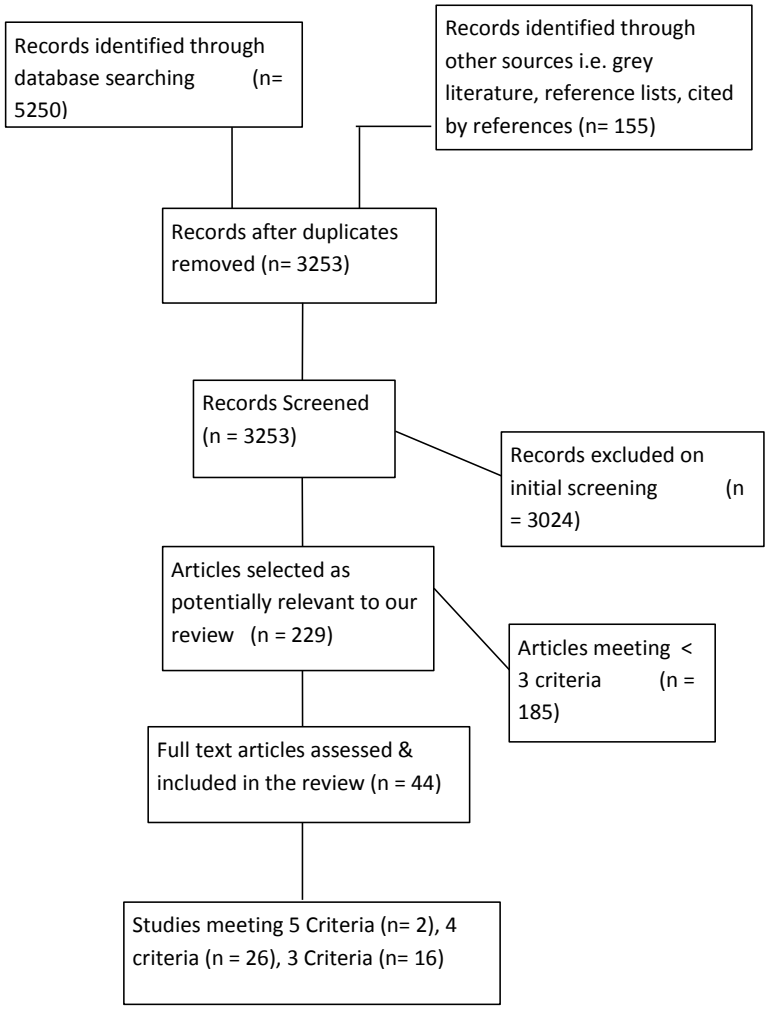
Criteria:-

1. The paper refers to BPD / Emotionally Unstable Personality Disorder (EUPD) as the primary diagnosis
2. Must be a case-control/ cohort/ cross sectional study or higher on the hierarchy of evidence
3. The population under investigation were all over 18 years of age
4. EEG was the only or main investigation of the study. Articles meeting criteria 4 must also refer to BPD or equivalent terms
5. The article refers to EEG changes during emotional fluctuations

Articles that met three or more of the above criteria were fully reviewed

	5 Criteria	4 Criteria	3 Criteria
Number of Papers	2 Papers	26 Papers	16 Papers

Search and elimination process



Articles meeting all 5 Criteria (n = 2)

Article	Diagnostic System	N (M /F)	Control group	Medications	Comorbid conditions	Findings
Beeney et. al. 2014 Response to Cyberball rejection task	SCID	23 (0/23)	Major depressive disorder (n= 13) Healthy controls (n= 21)	Not discussed	No depressive episode in last 6 months in test group but 66% and 38% of MDD controls had other MH conditions	Following rejection task individuals with BPD showed greater left cortical activation, those with MDD greater right cortical activation and HCs a more balanced cortical profile ($p<0.001$)
Russ et. al. 1999 EEG Response Between who report pain in self harm versus not	DSM-III-R and SCID	41 (0/41) BPD – P (n= 22) BPD –NP (n= 19)	Major depression Healthy controls (n =15)	Antidepressants, antipsychotics, mood stabilizers, benzodiazepines	High rate of Axis I and II co-morbidities especially affective disorders	Total theta power significantly higher in BPD-NP than depressive group ($p=0.0074$) and healthy controls ($p<0.0001$)

Articles meeting 4 criteria (n = 26)

One review identified discussed EEG findings in relation to BPD

1. Boutros et al. examined 26 articles on electrophysiological techniques in BPD. The authors performed MEDLINE and Psychinfo searches between 1966 to 2000 for “biological aspects” and “BPD”. They also performed additional searches using the terms EEG, evoked potentials (EP), sleep and polysomnography (PSG).

2. High prevalence of electrophysiological aberrations (such as shortened REM latency on polysomnography and diminution of P300 amplitude in evoked potential studies)

3. Heterogeneity between articles due to the complexity of the disorder, ambiguity of diagnostic criteria used, lack of control for comorbidity and pharmacotherapy

4. The reviewers conclude that the existing literature represents a preliminary stage

5. This study did not meet criteria 5 as it did not particularly highlight EEG changes occurring due to arousal fluctuations

Articles meeting 4 criteria (n = 26)

	Standard EEG	Sleep EEG	Evoked potentials
All	8	10	7
2000	2	4	3
	Hegerl et al.2008 - met criteria 5 Looking at vigilance state change BPD vs. HCs vs. OCD Van Elst et al. 2016 - significantly increased prevalence of intermittent rhythmic delta and theta activity BPD 96 vs. HCs 76	Assad et. al. 2002 De La Fuente, 2001 & 2004 Philipsen et. al. 2005 All 4 papers Shorter latency to REM Longer REM periods Higher REM density	inconsistent findings Meares et al. 2004 – Enhanced amplitude of P3a and loss of temporal synchronicity of P3a with P3b in BPD compared to HCs Marissen et al. 2010 – larger late positive potentials compared to HC He et al, 2012 – No difference in the effect of facial emotions on event related potentials in BPD compared to other groups including HCs

Articles meeting 3 Criteria (n =16)

Criteria	1,2,3	1,2,4	1,3,4	2,3,4	2,4,5
1. Primary Diagnosis 2. Type 1-3 evidence 3. Adults 4. EEG main investigation + BPD 5. Measure arousal fluctuation	6	3	1	5	1

Eleven showed EEG abnormalities in those with BPD compared to control

Two articles showed EEG abnormalities in children with histories of abuse and one article demonstrated EEG abnormalities in “psychoneurosis”

There was significant heterogeneity in methods and findings between articles meeting three criteria

So how do we use this evidence?

Identify common and/or relevant EEG findings from all studies

Put it into a “checklist”

Attempt to validate it in a new population

Possible Checklist factors

Q - EEG	Standard EEG	Sleep EEG	Evoked Potentials
Intrahemispheric and Interhemispheric coherence	Diffuse slowing	Increased REM percentage	Prolonged P300 latency
Absolute power (all waves) particularly Theta	Dysrhythmias	Increased REM density	Decreased P300 amplitude
Relative power (all waves)	Sharp waves, especially in posterior areas	Shorter REM latency	Increased amplitude of P3a and loss of temporal synchronicity of P3a with P3b.
Mean frequency	Increased slow wave activity	Longer REM period	Larger late positive potentials (LPP) to pictures with an unpleasant valence
Asymmetry values	Increased prevalence of intermittent rhythmic delta (IRDA) or theta (IRTA) activity	Reduced slow wave, stage 3 & 4 sleep	Higher loudness dependence of the N1/P2 component of auditory evoked potentials
Greater left cortical Activation	Abnormalities in Temporal areas	Increased delta power in Non-REM sleep	Reduced P3 amplitudes during No -Go responses in Go-No -Go test
			Smaller LPC amplitude
			Enhanced activation of the orbitofrontal cortex following an unexpected reward in BPD with NSSI.
			Delay in early posterior gamma synchrony & reduced right hemisphere late gamma synchrony
			Increase in slow wave frequencies (theta, delta and slow alpha) in the orbital cortex, dorsomedial prefrontal and dorsolateral prefrontal cortexes and a decrease of fast wave activities

Possible Checklist factors

Q - EEG	Standard EEG
Intrahemispheric and Interhemispheric coherence	Diffuse slowing
Absolute power (all waves) particularly Theta	Dysrhythmias
Relative power (all waves)	Sharp waves, especially in posterior areas
Mean frequency	Increased slow wave activity
Asymmetry values	Increased prevalence of intermittent rhythmic delta (IRDA) or theta (IRTA) activity
Greater left cortical Activation	Abnormalities in Temporal areas

Overview of Transcranial Direct Current Stimulation

tDCs

Ohm’s Law

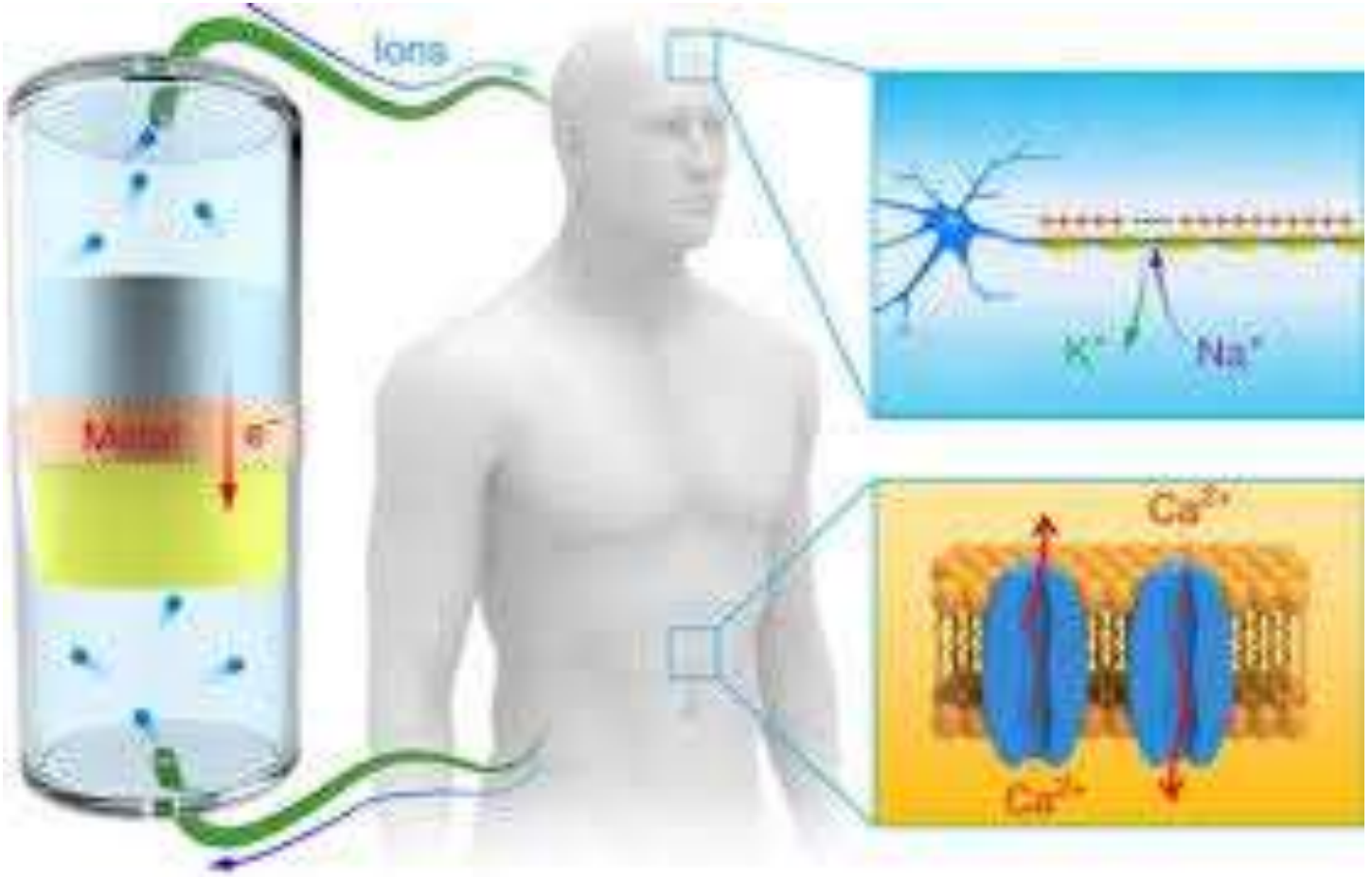
- Voltage can be thought of as the force that pushes electric current through the body. Depending on the resistance, a certain amount of current will flow for any given voltage. *It is the current that determines physiological affects*. Ohm's law is as follows:

- Voltage causes current (*I*) to flow through a given resistance (R). The somewhat circular current path is referred to as a circuit.

Currents can also flow via charged Ions

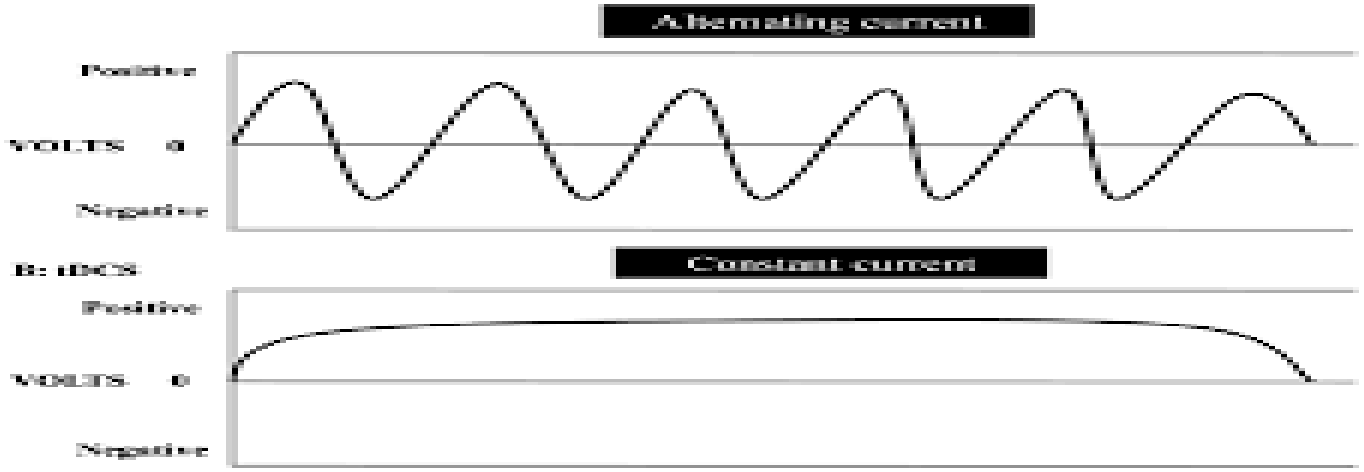
- Most metals are examples of good conductors. Copper and silver are particularly good conductors, and this is the reason why they are used in electrical wiring.
- Glass, mica, and porcelain, as well as most plastics, are examples of poor conductors or good insulators.
- **Electric currents also can flow in liquid media such as solutions. In such cases, the particles carrying the electrical charge are ions.**

Ion flow results from DC current stimulation



DC and AC Current

- Direct current is current in which the flow of electrons is in one direction only.
- It results when you apply a steady voltage to a circuit. Batteries are the most common source of DC
- Alternating current or AC is a pulsating or fluctuating electric current that alternately flows in one direction and then in another.



Impedance

- Impedance of an R-C circuit is the combined effect that the two parameters of resistance and capacitance have on the flow of current produced when an alternating voltage is applied to the circuit.
- Mathematically, impedance is equal to Z where R is the value of resistance in ohms, C the value of capacitance, f the frequency of the alternating voltage in Hz.

$$Z = \sqrt{R^2 + \left(\frac{10^6}{2\pi f C}\right)^2}$$

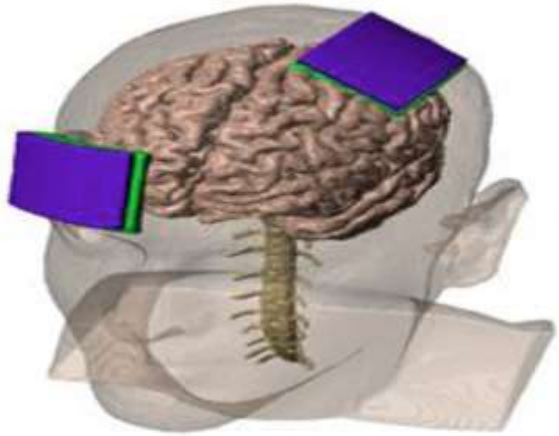
Summary

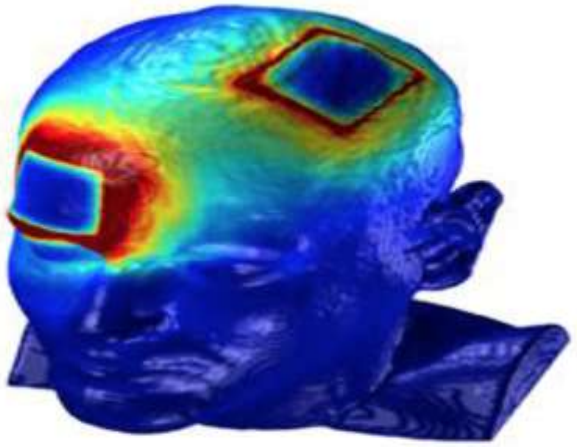
- *Current* refers to the amount of electricity (electrons or ions) flowing per second.
- Current is measured in amperes or milliamperes (1 mA=1/1000 of an ampere).
- The amount of electric current that flows through the body determines various effects of the modality.
- The body has *resistance* to current flow.

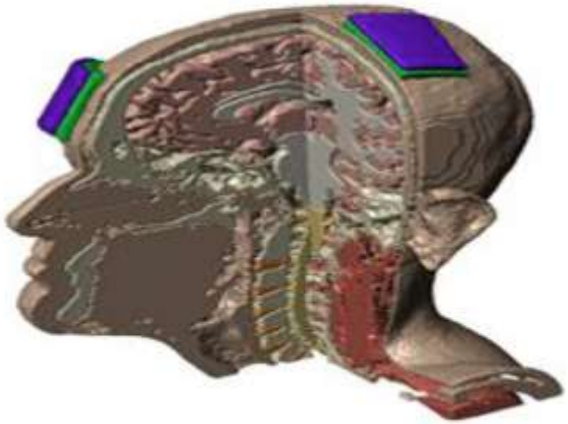
Resistance

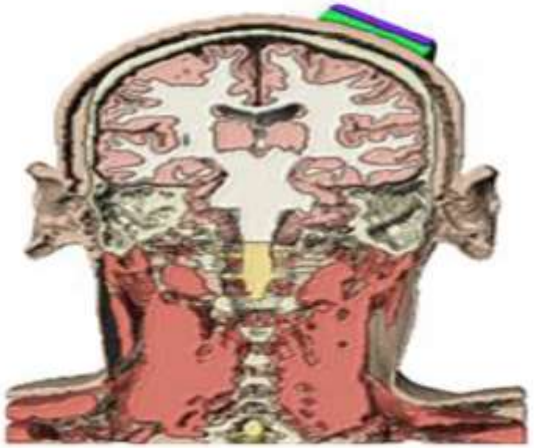
- More than 99% of the body's resistance to electric current flow is at the skin.
- Resistance is measured in ohms.
- A calloused, dry hand may have more than 100,000 Ω because of a thick outer layer of dead cells in the stratum corneum.
- The internal body resistance is about 300 Ω, being related to the wet, relatively salty tissues beneath the skin.
- The skin resistance can be effectively bypassed if there is skin breakdown from high voltage, a cut, a deep abrasion, or immersion in water

tDCs Application









tDCs today

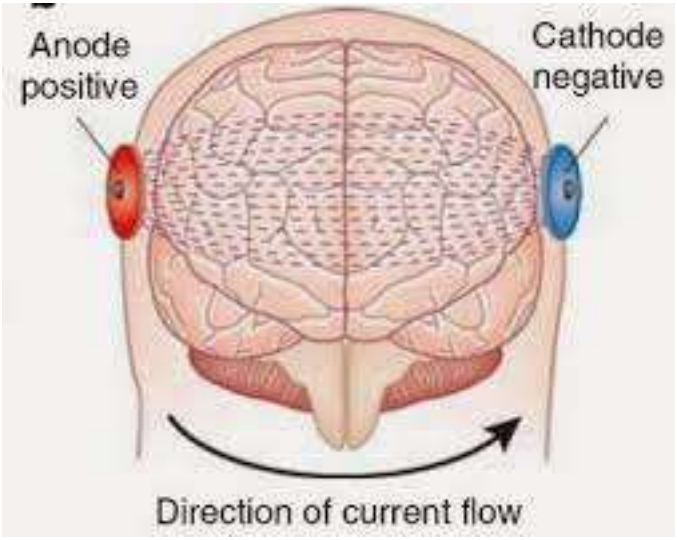
- Certain appealing characteristics of tDCS (such as the fact that it is noninvasive and has mostly well-tolerated, transient, and mild adverse effects) have sparked a recent increase in clinical studies.
- DC has since been used in the treatment for disorders such as:
- major depressive disorder,
- chronic and acute pain,
- stroke rehabilitation,
- drug addiction,
- other neurologic and psychiatric conditions.

What is tDCs?

- tDCS is defined as a technique in which the dose is a waveform of single sustained direct current (DC), with the exception of one ramp-up and one ramp-down period, applied to the head using at least one cephalic electrode.
- tDCS is non-invasive and requires appropriate electrolyte buffer (conductive gel, paste, or saline) between the electrode and the skin.
- tDCS thus does not include the use of subdural stimulation electrodes.

Current Flow

- Any electrode from which current enters into the body is an anode, and any electrode where current exits the body is a cathode.
- tDCS/DCS must have at least one anode electrode and one cathode electrode.



Important Clinical Points

- Under either polarity electrode, the direction of measured excitability changes can vary with brain state and dose parameters such as stimulation intensity and duration.
- Clinically it is essential to understand how these parameters alter the current flow.

Intensity and Duration

tDCS/DCS intensity (in amperes, A or mA) is the steady-state intensity applied to the anode.

If multiple electrodes are used, intensity is the sum of the current at all anodes.

tDCS/DCS duration (in seconds or indicates the length of time

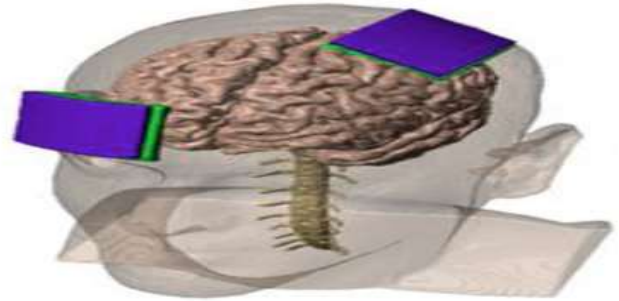
current is at the steady level, and

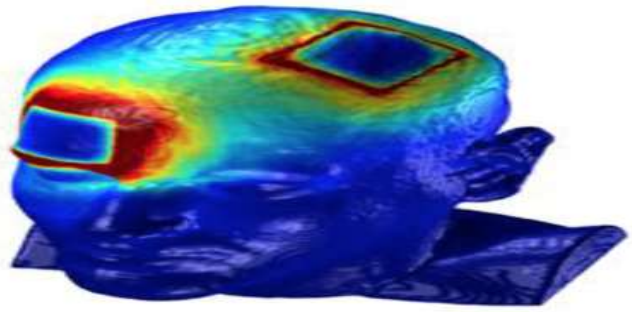
ramp-up and ramp-down

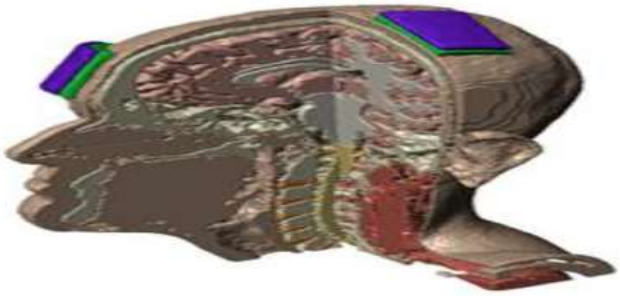
periods.

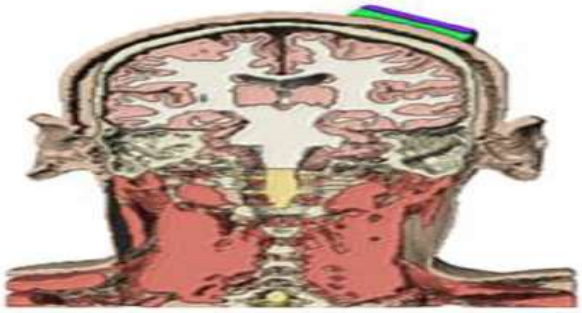
Dose Calculation

- The dose of a single tDCS/DCS session is defined by the electrode montage (skin contact area/size and position of all electrodes), stimulation intensity and duration.
- tDCS/DCS is current controlled, meaning the voltage is varied to maintain a fixed current.







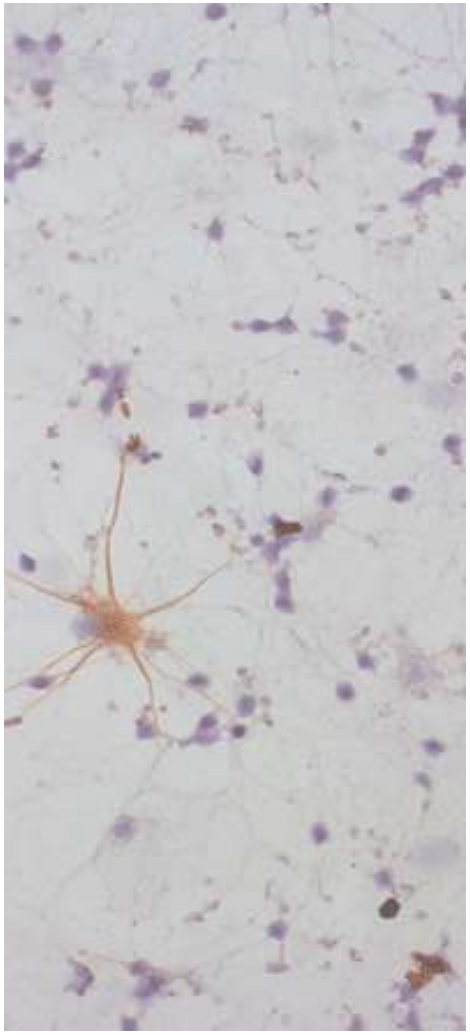


How does DC work?

- TDCS does not induce neuronal firing by suprathreshold neuronal membrane depolarization but rather modulates spontaneous neuronal network activity at the neuronal level
- the primary mechanism of action is a tDCS polarity-dependent shift (polarization) of resting membrane potential.
- Although anodal DCS generally enhances cortical activity and excitability, cathodal DCS has opposite effects.

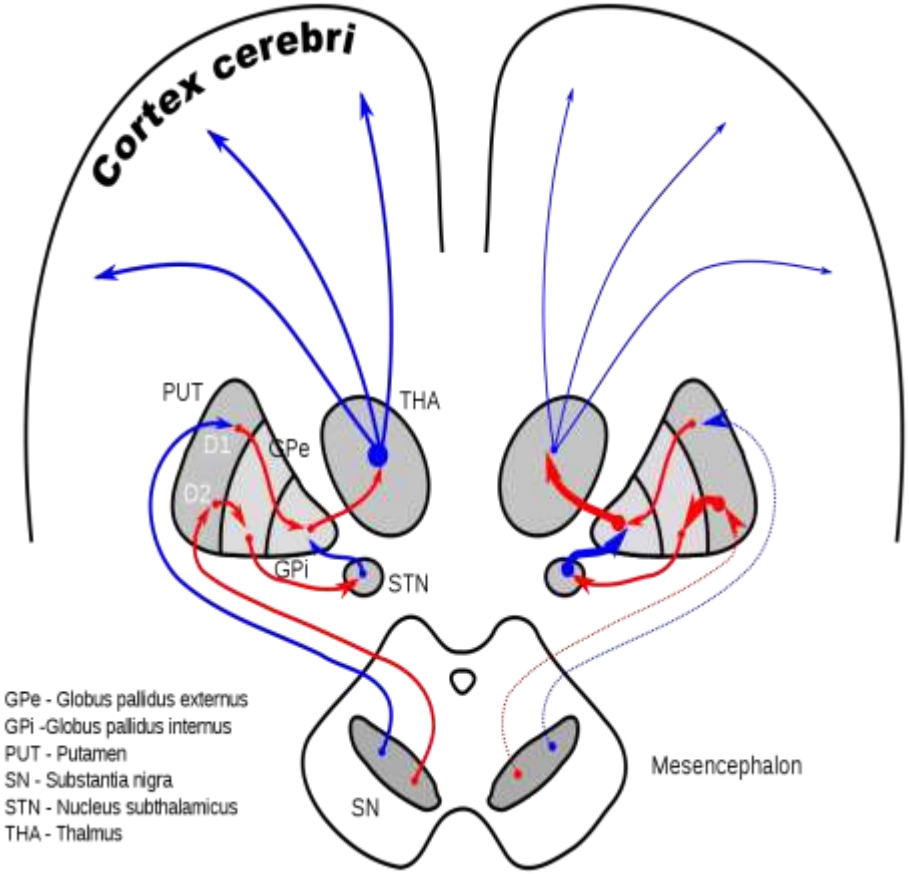
Neurophysiology of tDCs

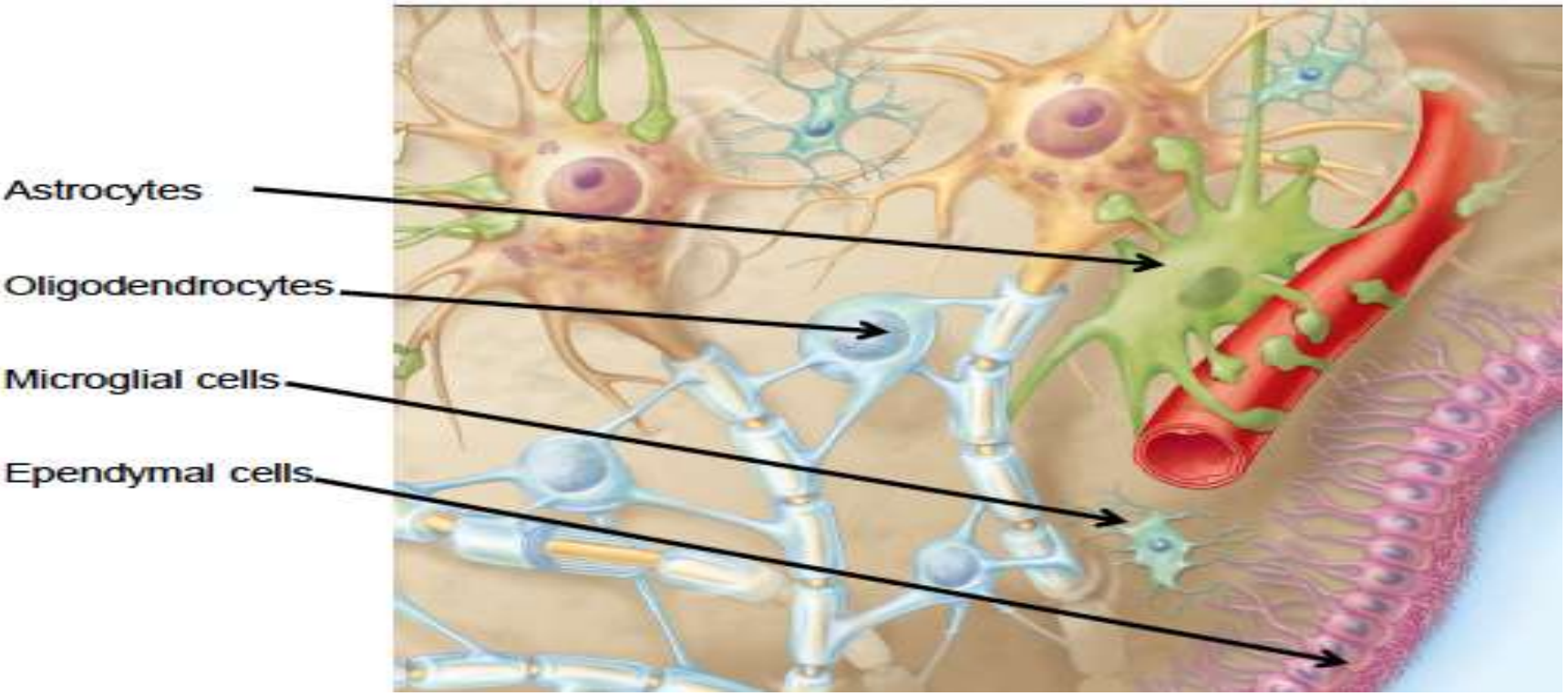
- tDCS elicits after-effects lasting long after the stimulus has ceased. Therefore, its mechanisms of action cannot be solely attributed to changes of the electrical neuronal membrane potential.
- In fact, further research showed that tDCS also modifies the synaptic microenvironment, for instance, by modifying synaptic strength NMDA receptors or altering GABAergic activity.



Direct and Indirect Affects

- In addition to the ‘‘direct’’ tDCS effects described previously, ‘‘indirect’’ effects are also observed.
- This is seen in connectivity-driven alterations of distant cortical and subcortical areas.



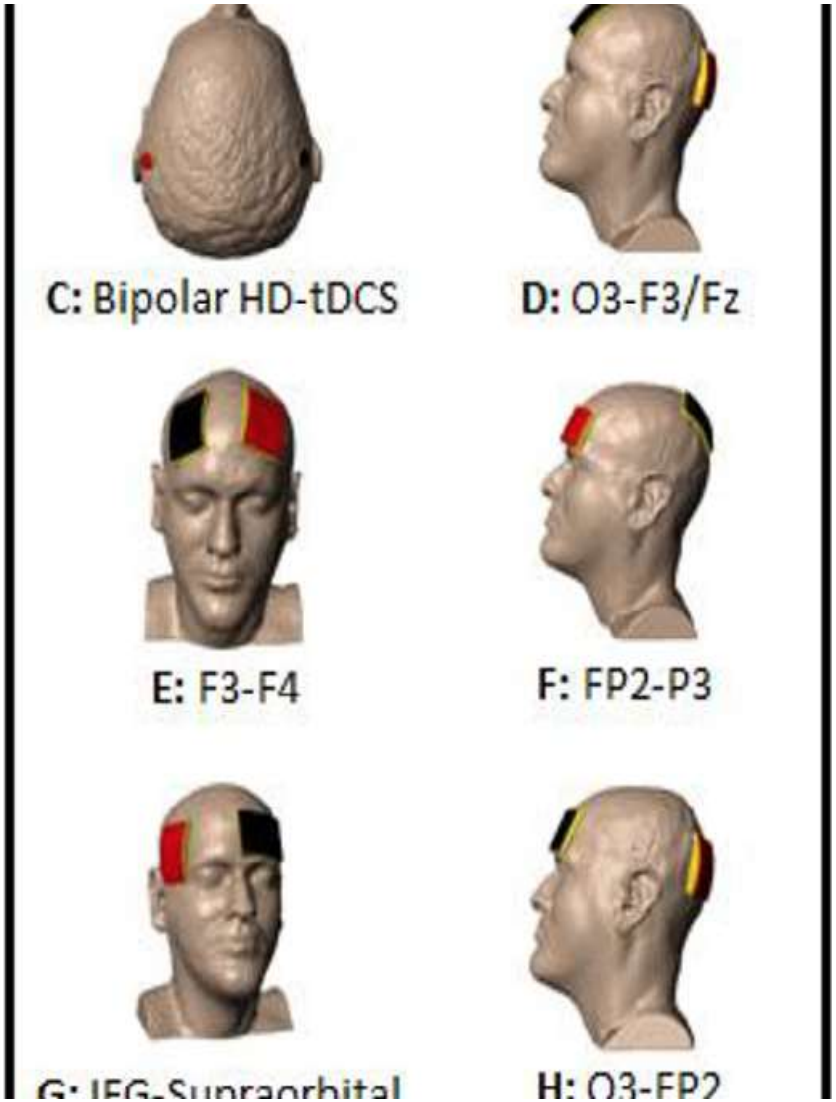


Constant electrical fields influence several different tissues (vessels, connective tissue) and pathophysiologic mechanisms (inflammation, cell migration, vascularmotility)

The effects are also observed on multiple cellular structures (cytoskeleton, mithocondria, membrane).

Electrode Montage

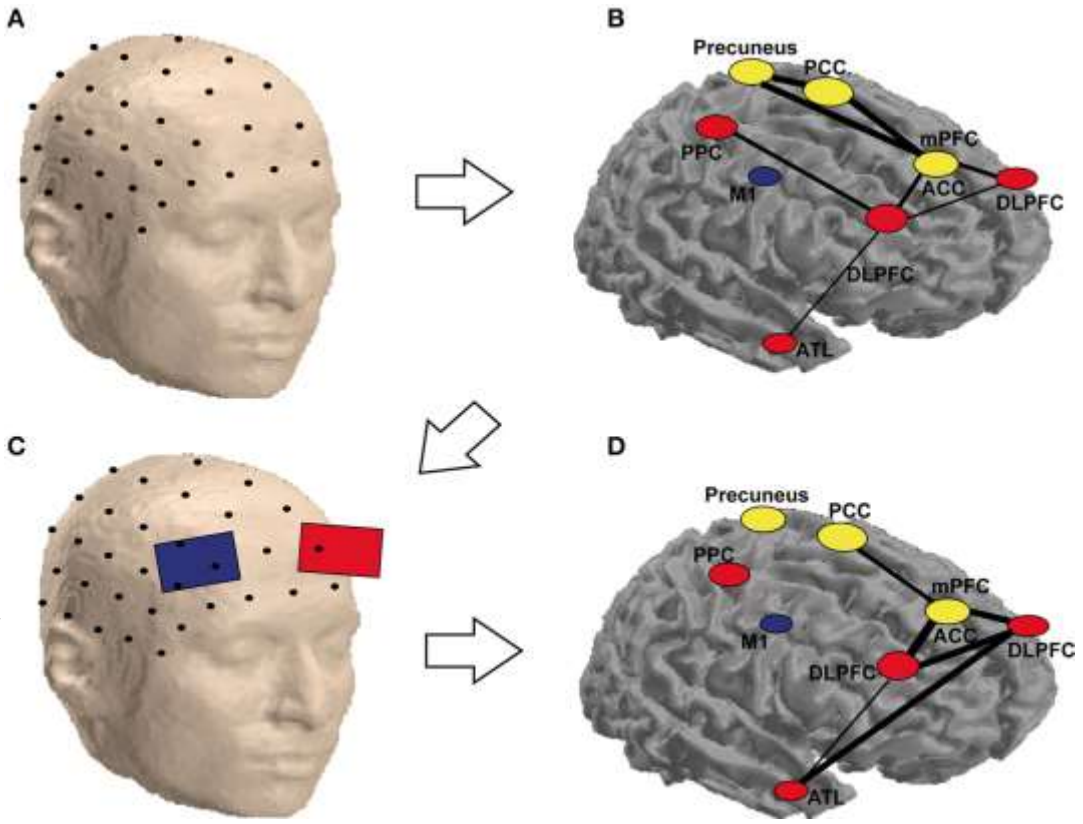
- Electrode montage is critically associated to the amount of current being shunted through the skin, how much is delivered to the brain, and to what targets.



- TDCS studies usually use one anode and one cathode electrode placed over the scalp to modulate a particular area of the CNS.
- Electrode positioning is usually determined according to the International EEG 10-20 System.

Clinical Application

- Having the possibility to increase and decrease activity in different brain areas simultaneously may be advantageous.
- For instance, this could be useful in conditions involving an imbalanced interhemispheric activity (ie, stroke, depression, seizure disorder)



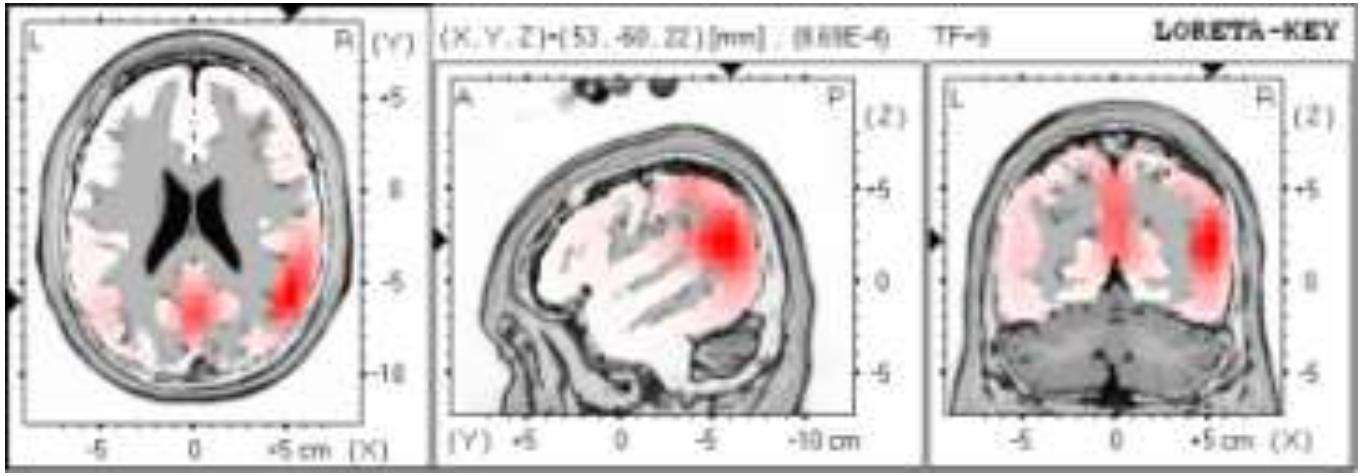
Combination Therapy

- EEG/LORETA targeted Transcranial Direct Current
- Nutritional Supplementation
- Home Stimulation Program

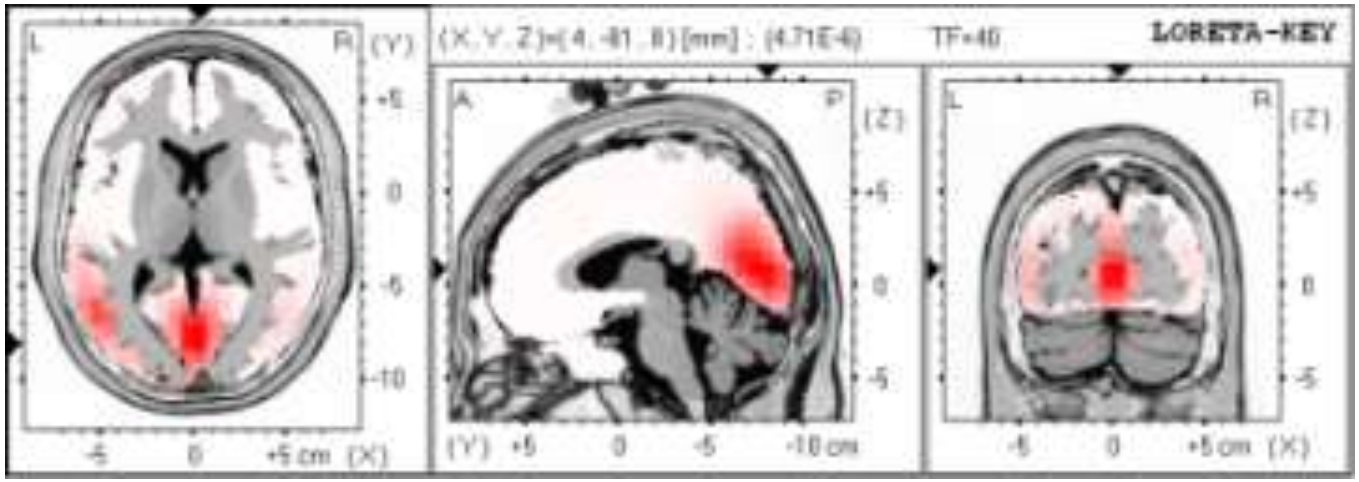
Post traumatic seizures

- Post traumatic seizures can occur following head trauma, stoke or a variety of other lesions.
- Post traumatic seizures are also known as scar epilepsy and are often medically non-responsive.

LORETA Targeted tDCs and Seizure Activity



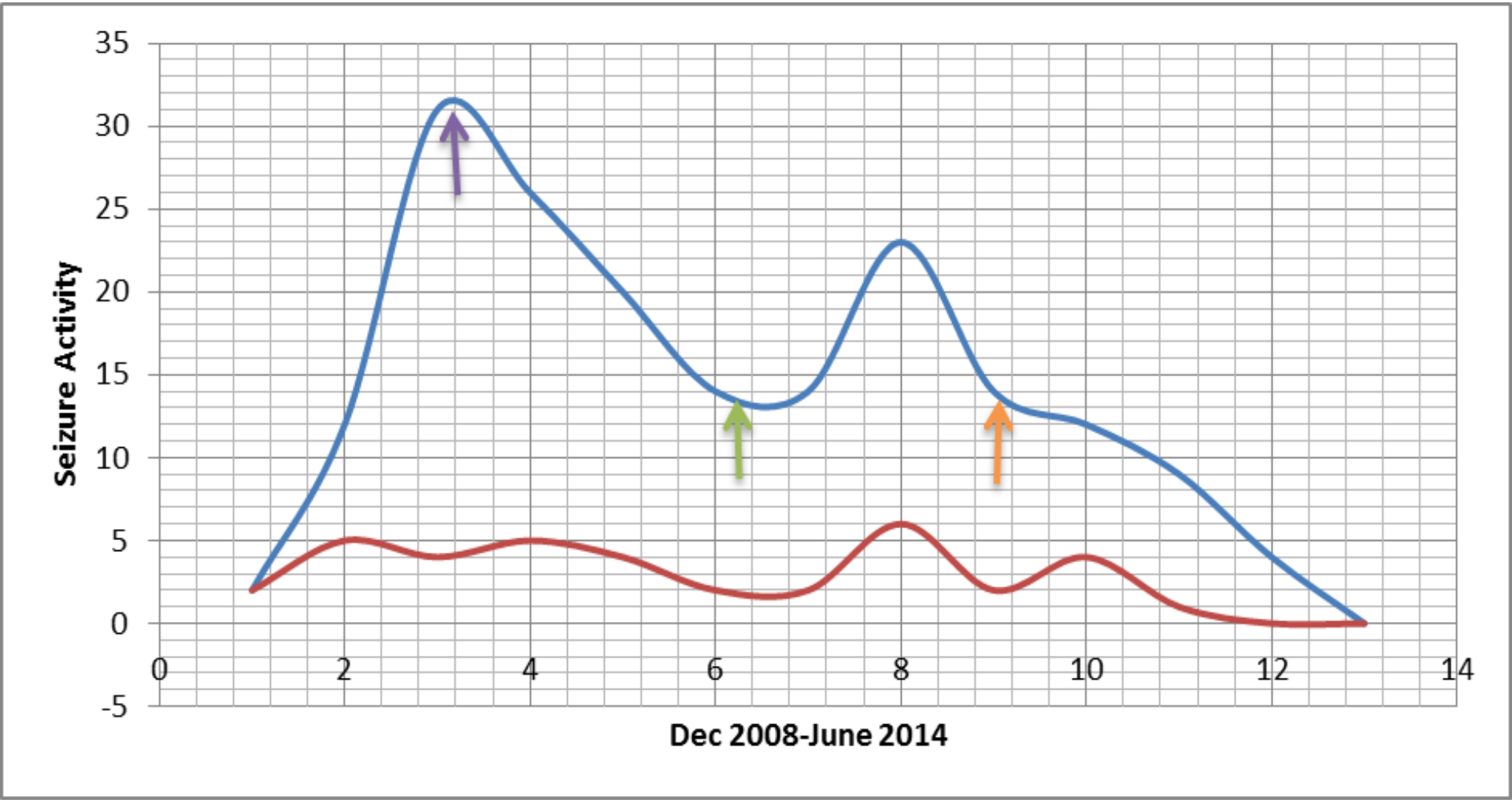
Patient DP
Before



Patient DP
After

Beck, RW. Integrative Medicine: 2012

Seizure Activity 2008-2014



Blue Line: Any Seizure Activity; Red Line: Major Myoclonic Seizure;
Purple Arrow: Institute Tx Starts
Green Arrow: Lamictal stopped; Orange Arrow: Tegretol stopped

Combination Therapy

- EEG/LORETA targeted Transcranial Direct Current
- EEG/LORETA targeted Peripheral Stimulation
- Nutritional Supplementation
- Home Stimulation Program

Overview

Major depression disorder (MDD) is characterized by:

- dysphoric and irritable mood,
- rumination and self-referential thinking,
- anhedonia,
- a loss of motivation and interest in daily activities
- impaired functioning in the social and occupational domains

(American Psychiatric Association, 2013)

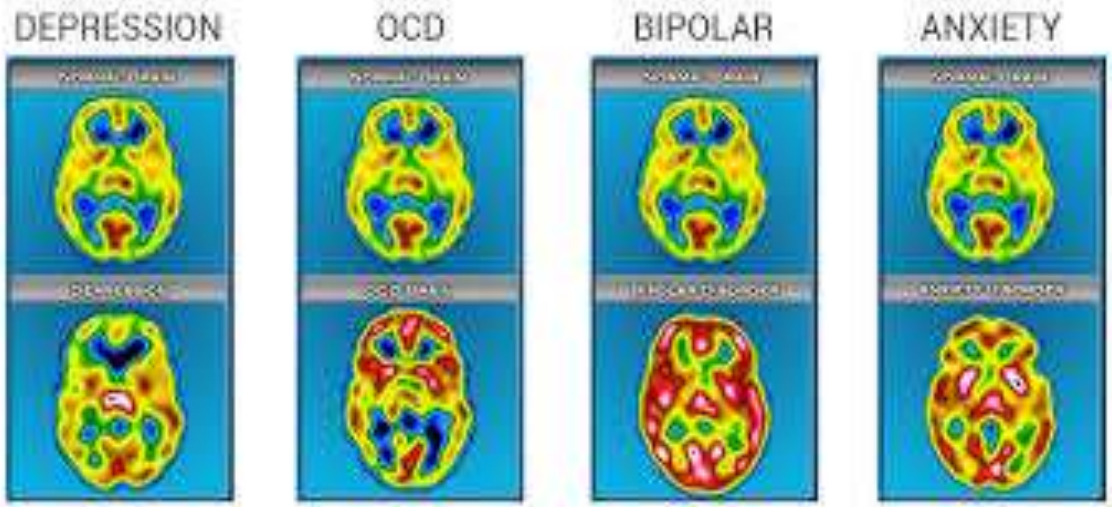
Morbidity

- MDD is a complex mental illness that can result in significant disability, reduced quality of life, and societal burden affecting 10%–15% of the population per year

Al-Harbi KS. Treatment Resistant Depression: Therapeutic Trends, Challenges, and Future Directions. Patient Preference and Adherence 2012:6 369–388

Structural and Functional Biomarkers

A major theme emerging from recent studies is that structural and functional changes in activity levels in a variety of brain regions may be used as biomarkers to indicate levels of severity and location of dysfunction in MDD and other psychiatric disorders.



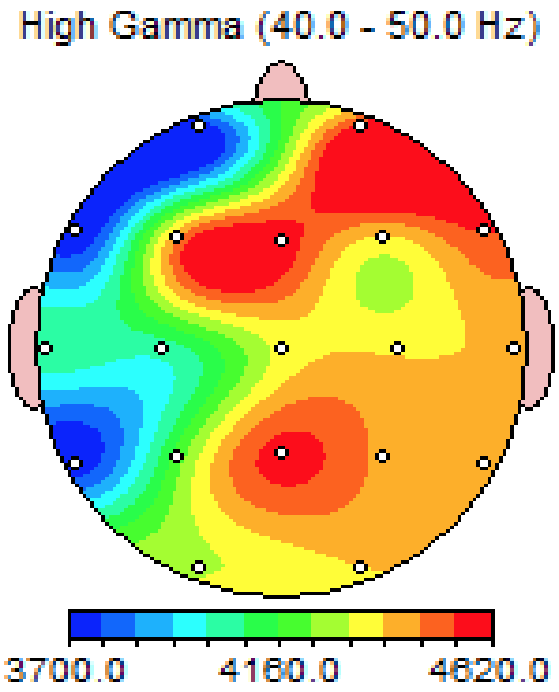
Davidson's Conceptual Model

- A variety of research approaches have focused on individual differences in EEG asymmetry patterns, following Davidson's conceptual model which suggested that individual differences in asymmetry patterns may be associated with a tendency towards certain affective styles and may be related to the individual's susceptibility to develop depression

- (Davidson, 1998; Fingelkurts and Fingelkurts, 2015; Thibodeau et al., 2006).

Cortical Asymmetry

- Individuals showing decreased left frontal activity or enhanced right frontal activity are more likely to experience feelings of sadness and anhedonia or to exhibit behavioral inhibition and withdrawal, all of which are known to be associated with depression, in addition to other psychiatric conditions.
- (Sutton and Davidson, 1997)



Case A

A 39yr old married woman with one infant child. Presents with long term symptoms of anxiety and depression of a mild-moderate severity. Diagnosed with Dysthymia and Generalised Anxiety Disorder. Not keen on medications so unmedicated but several brief periods of supportive counseling and CBT based psychotherapy in previous years.

Case B

A 52yr old unemployed divorced woman with 3 adult children. Presents with a 20yr history of symptoms of anxiety and depression. A significant trauma history and re-experiencing and avoidance symptoms noted. Diagnosed with chronic PTSD and Major Depressive Disorder. Currently prescribed Sertraline 200mg daily (for several months). Previous trials of several antidepressants and CBT based psychological interventions.

Case C

A 47yr old married woman with one adult daughter. Employed part-time as a nurse. Gives a 25 yr history consistent with a diagnosis of Major Depression with psychotic symptoms. Multiple trials of medications over previous years and courses of CBT based psychotherapy.

- Current medications: Efexor SR 450mg, Mirtazapine 30mg, Quetiapine 325mg, Diazepam 5mg BD, Risperidone 4mg.

Case D

A 28yr old single unemployed woman living with her mother who acts as her carer. She gives a 13yr history of psychotic symptoms and has been given clinical diagnoses of Schizophrenia, PTSD, Autism spectrum disorder and Major Depression. Ongoing psychological therapy and social supports are in place.

- Current medications: Olanzapine 25mg, Asenapine 20mg, Lamotrigine 450mg, Sertraline 100mg.

Method

- The participants in this study were all females ranging in age from 26-53 years of age with an average age of 40.5 years.
- All were examined by a registered psychiatrist and classified as a form of Major Depression.
- Treatment periods ranged from 4-5 months with an average treatment period of 4.5 months.
- The participants each received a total of 54 clinical interventions during this period.

Self-administered Checklists

We utilized two psychometric tests as objective measure questionnaires to measure symptoms of psychopathology.

- the Depression Anxiety Stress Scale (DASS),
- the WHOQOL-BREF Assessment

Intervention

- Participants then received appropriate peripheral stimulation and tDCs stimulation as determined by the activity measured on their EEG.
- They received peripheral stimulation 3 times per week for 18 weeks.
- The EEGs, psychometric testing and treatment plan updates were performed at 18, 36 and 54 treatments.

Results

Chart 1 Group Ave Symmetry Ratio Fp1/Fp2

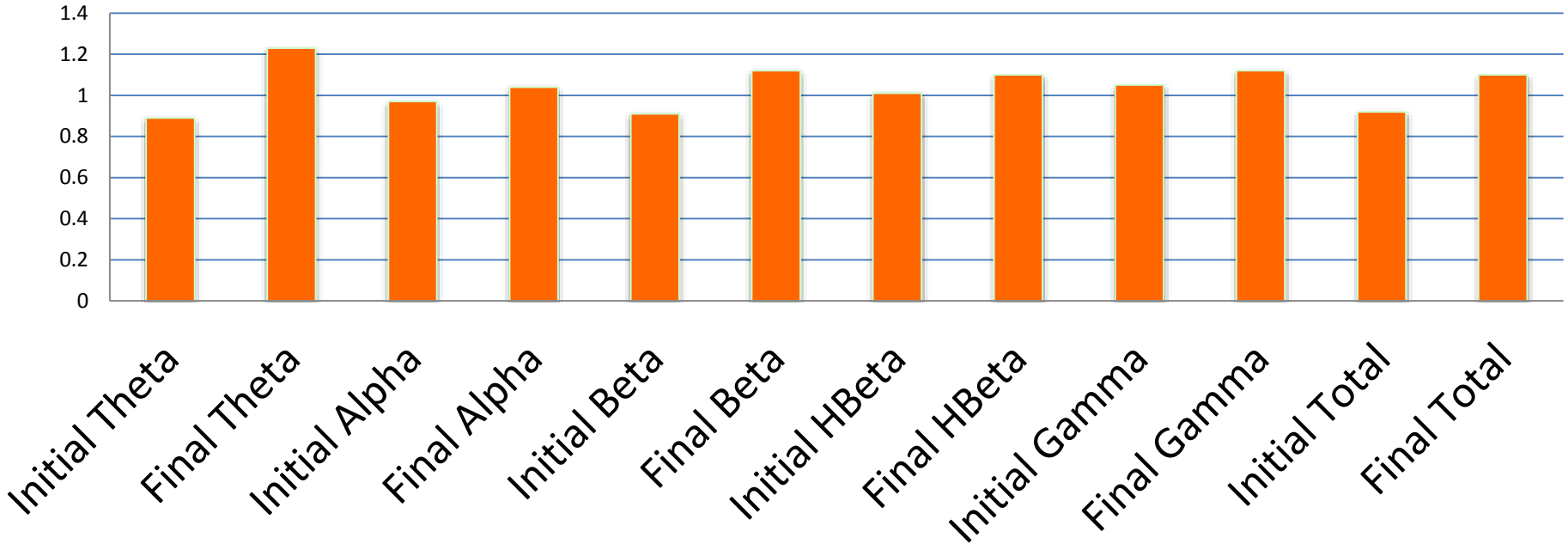
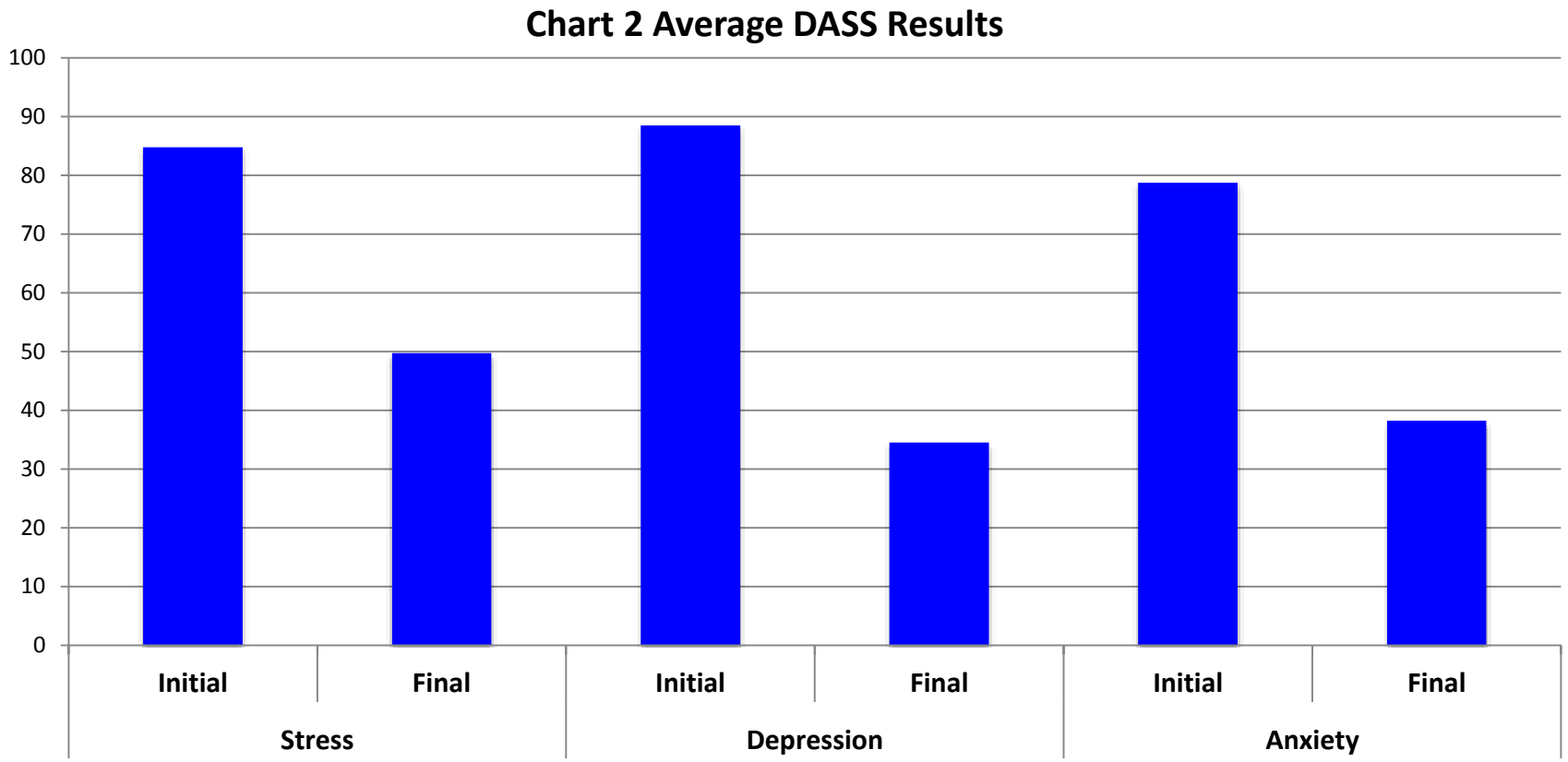


Chart 1 shows the average Fp1/Fp2 ratios of activity measured over all participants.

An Fp1/Fp2 ratio less then 1 indicates a right prefrontal cortex dominant asymmetry and a Fp1/Fp2 ratio greater than 1 indicates a left prefrontal cortex dominant asymmetry.

In all frequency ranges a shift from a right dominant asymmetry to a left dominant asymmetry was observed.



- **All participants demonstrated significant changes across all DASS categories;**
- **Stress (p=0.05),**
- **Depression (p=0.02)**
- **anxiety (p=0.01).**

The greatest percentage change was observed in the depression category (54%), followed by anxiety (40%) and stress (34%) respectively.

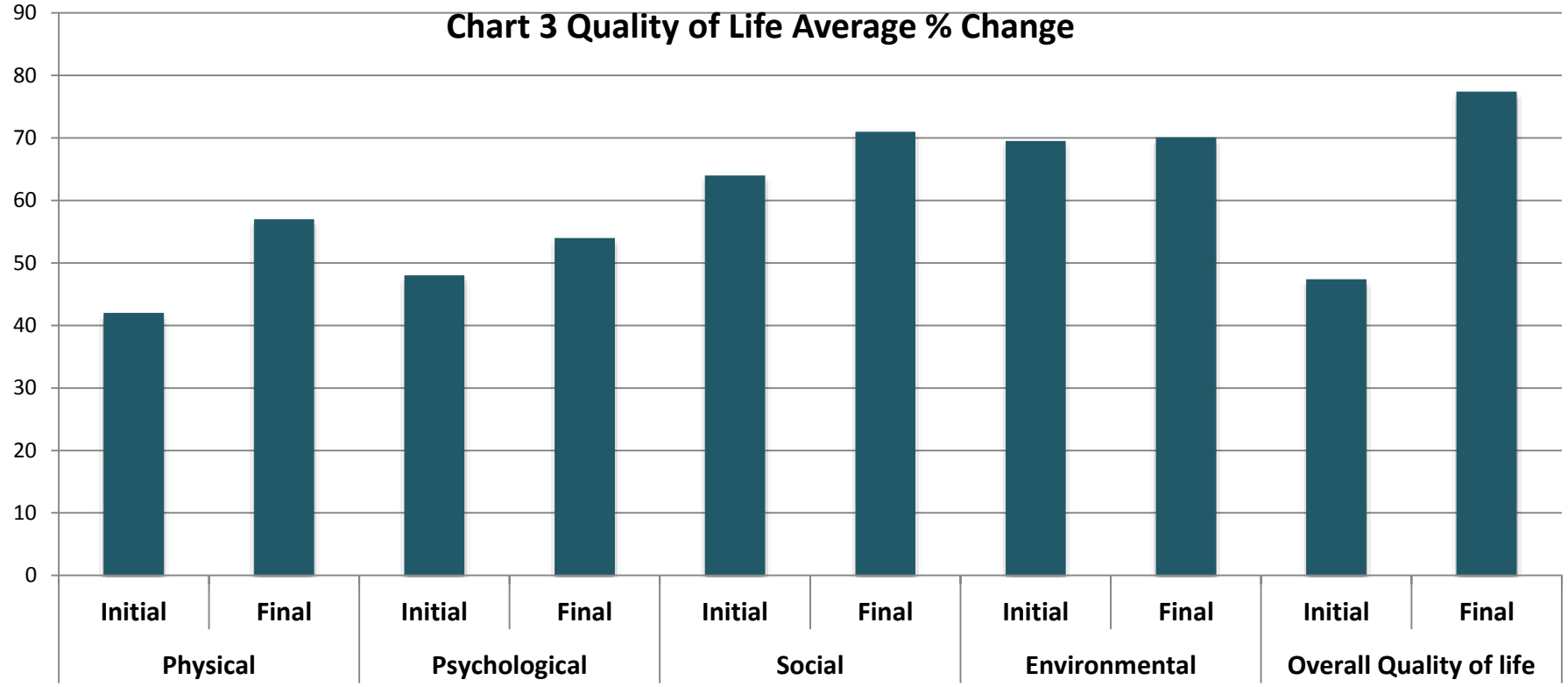
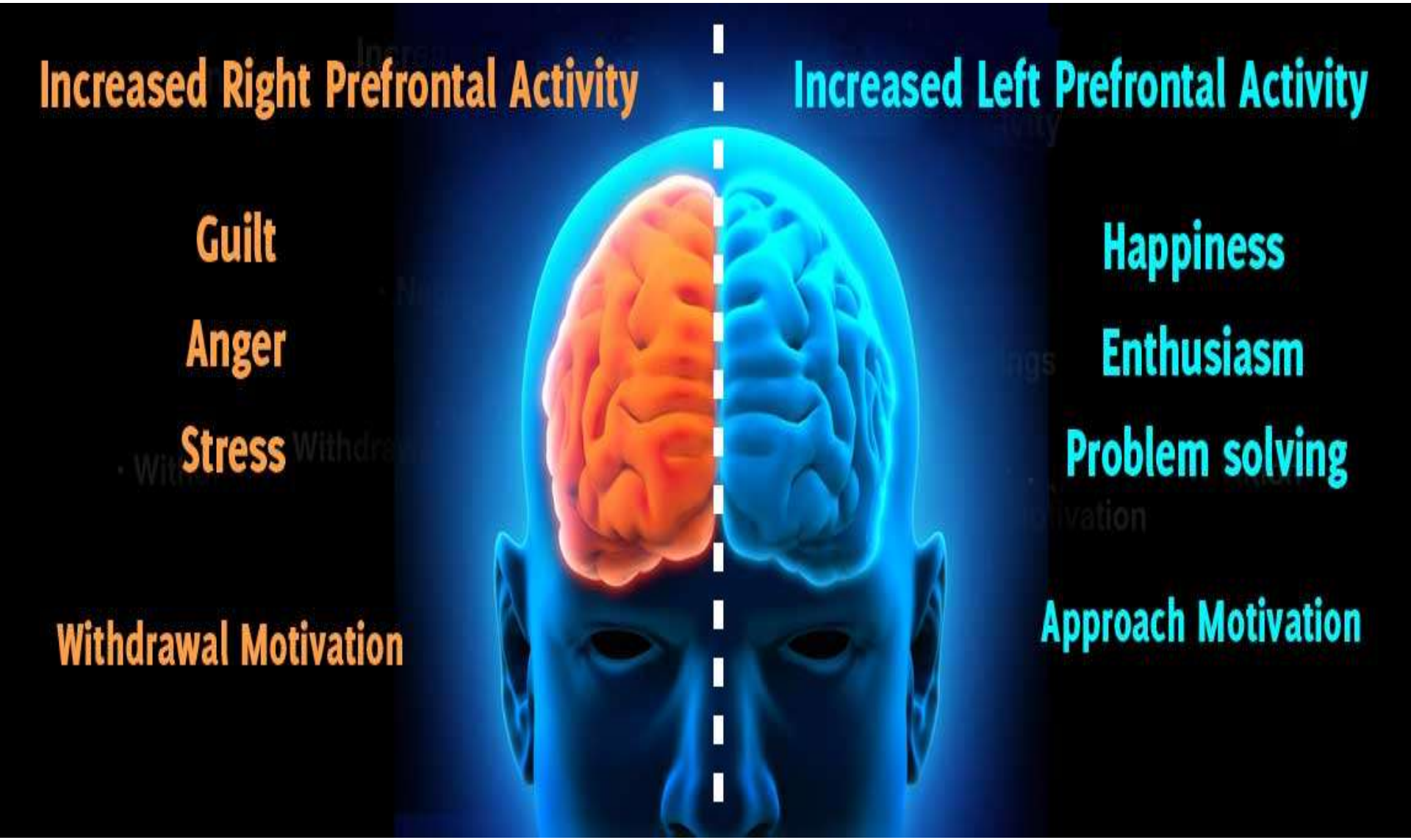


Chart 3 demonstrates the average percentage change in each WHOQOL-100 category. Positive changes were recorded in all categories.

Significant changes were recorded in the physical (p=0.04) and overall health categories (p=0.02).

Summary


Increased Right Prefrontal Activity
Guilt
Anger
Stress
Withdrawal Motivation
Increased Left Prefrontal Activity
Happiness
Enthusiasm
Problem solving
Approach Motivation

Conclusion

Our results indicate that EEG guided specific peripheral stimulation and tDCs can modulate cortical asymmetry across a variety of frequency ranges and that this modulation is associated with a significant change in symptom presentation as measured by psychometric self-reporting tools.

Overview of Transcranial Laser Stimulation

Low Level LASER Therapy (LLLT)

- Referred to as ‘‘low level’’ or “cold laser” because of its use of light at energy densities that are low compared to other forms of laser therapy that produce heat and are used for ablation, cutting, and thermally coagulating tissue.
- Low-level laser light therapy (LLLT) is the application of light in the red or near-infrared spectrum (600–1000 nm) at a power density between 1 and 5W/cm2

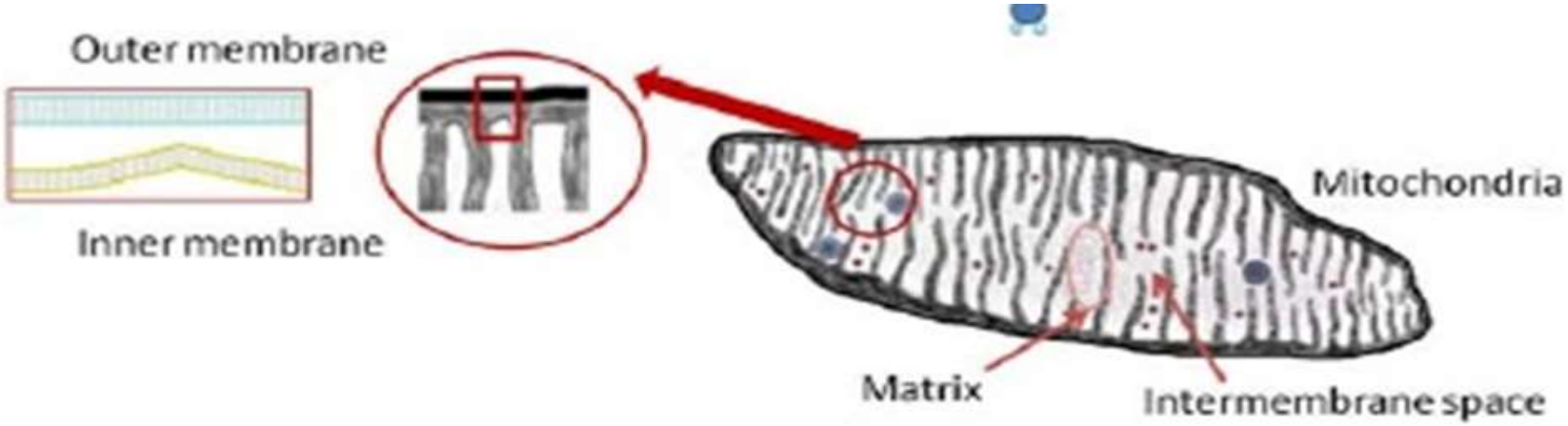
Neuromodulatory or Photobiomodulation action of red to near-infrared light wavelengths

- Based on the principle that certain molecules in living systems absorb photons and trigger signalling pathways in response to light.
- When a photon of light is absorbed by a chromophore in cells, an electron in the chromophore can become excited and jump from a low-energy orbit to a higher-energy orbit

  (Karu, 1987)
- This stored energy can then be used by the system to perform various cellular tasks

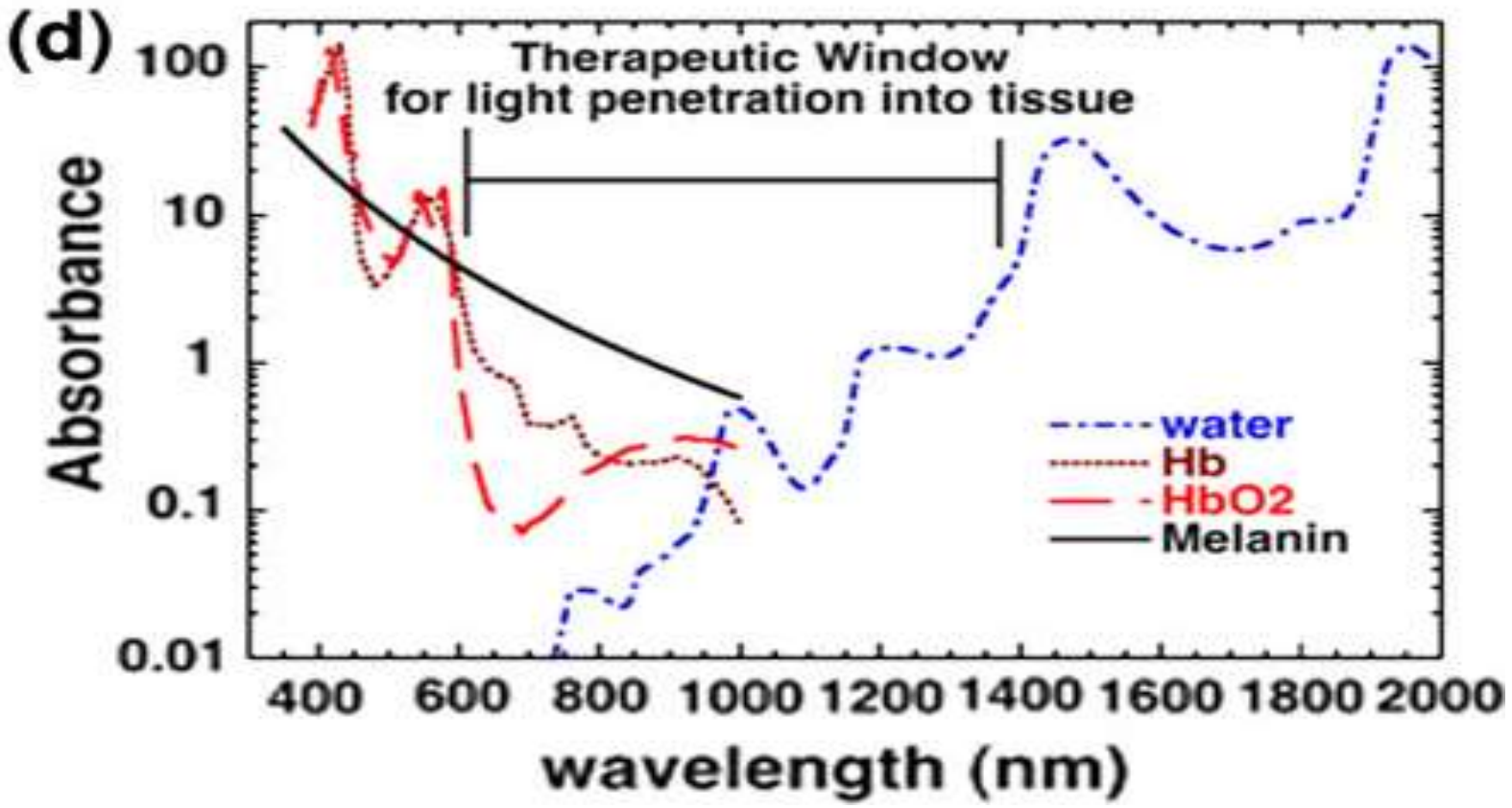
  (Sutherland, 2002)

Mitochondrial cytochrome oxidase appears to be one of the primary molecular chromophores



Cytochrome oxidase is the primary photo acceptor of red to near infrared light energy

- It is the enzyme responsible for catalysing oxygen consumption in cellular respiration
- Responsible for the production of nitric oxide under hypoxic conditions



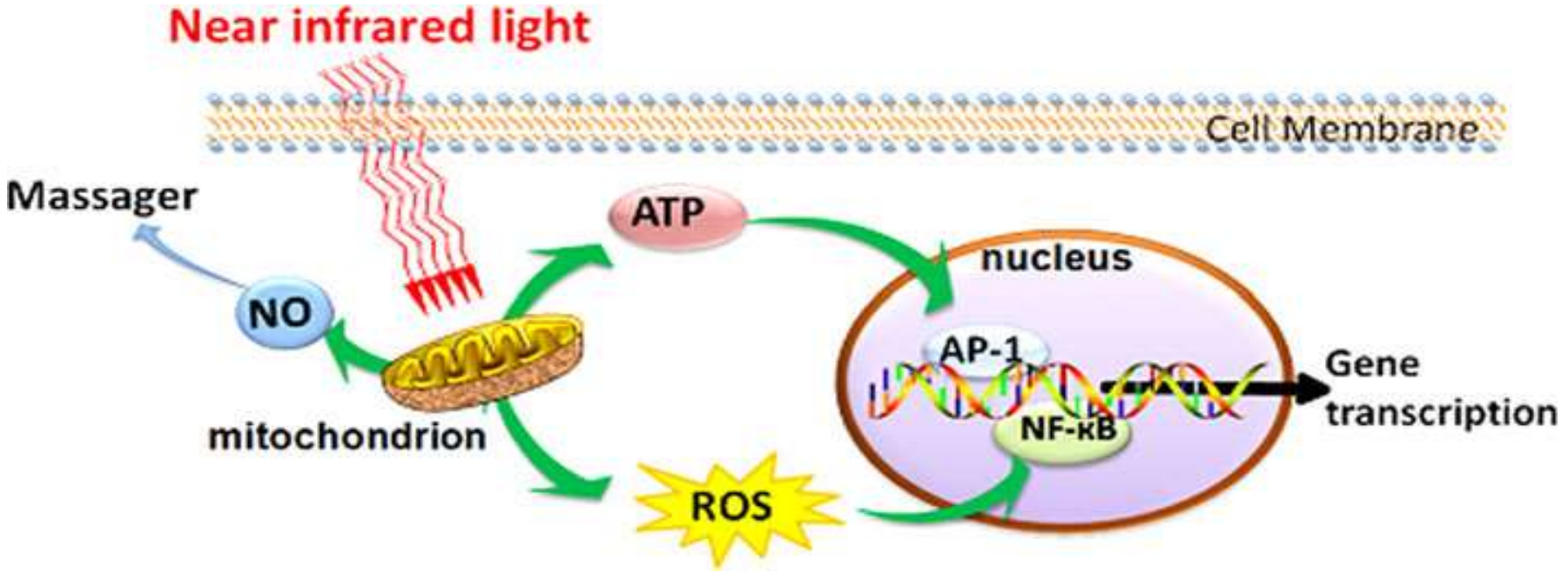
from Chung et al.,2012

There is a ‘‘**wavelength window**’’ for biologic stimulation that covers the red to near-infrared light spectrum (between 600 and 1150 nm)
(Hamblin and Demidova, 2006)

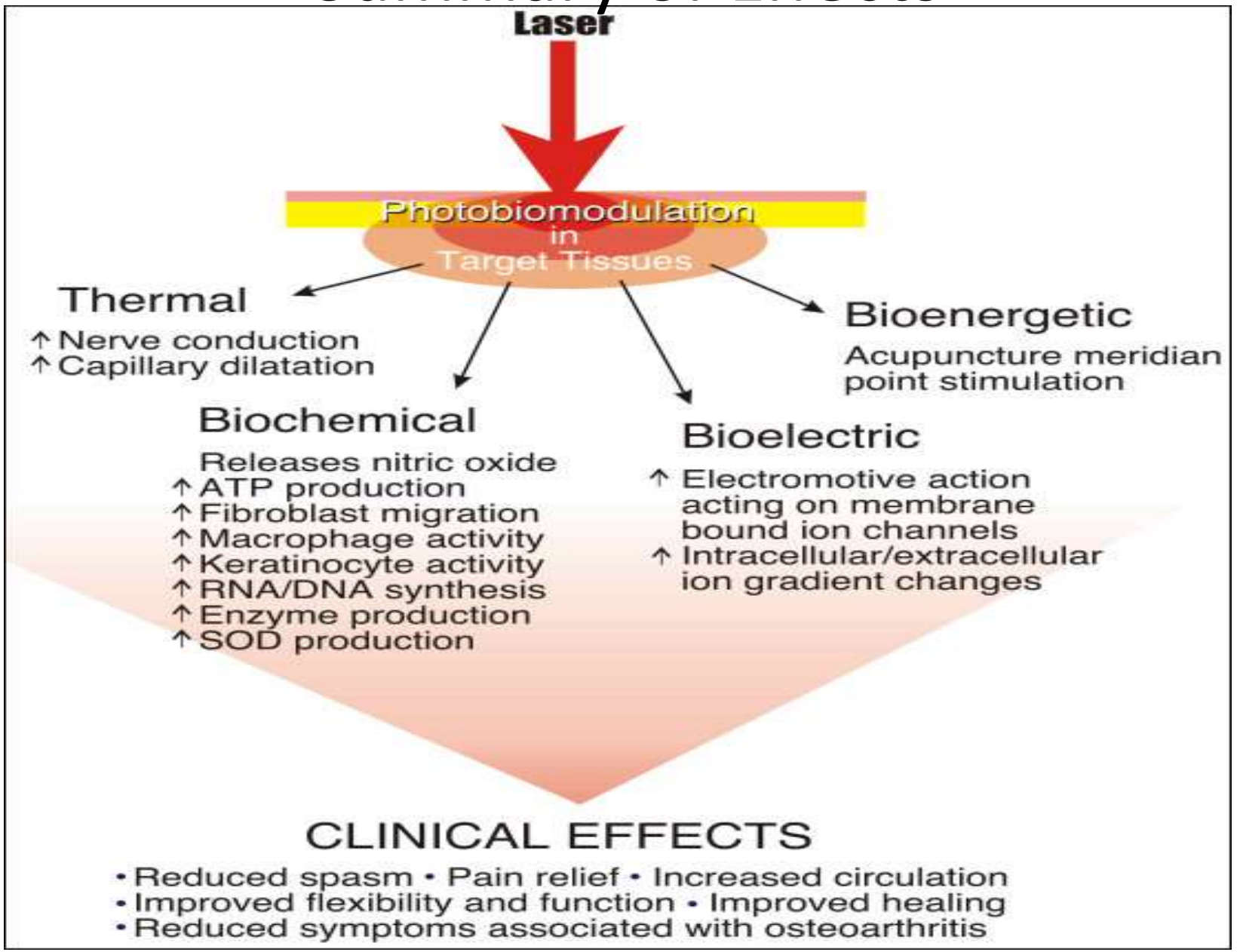
Strong evidence suggests that LLLT acts on the Mitochondria

- Increase adenosine triphosphate (ATP) production (Karu,1999)
- Modulation of reactive oxygen species (ROS),
- Induction of transcription factors

(Chen,2009)



Summary of Effects



Combination Therapy

- EEG/LORETA targeted Transcranial Laser
- EEG/LORETA targeted Transcranial Direct Current
- EEG/LORETA targeted Peripheral Stimulation
- Nutritional Supplementation
- Home Stimulation Program

Autism

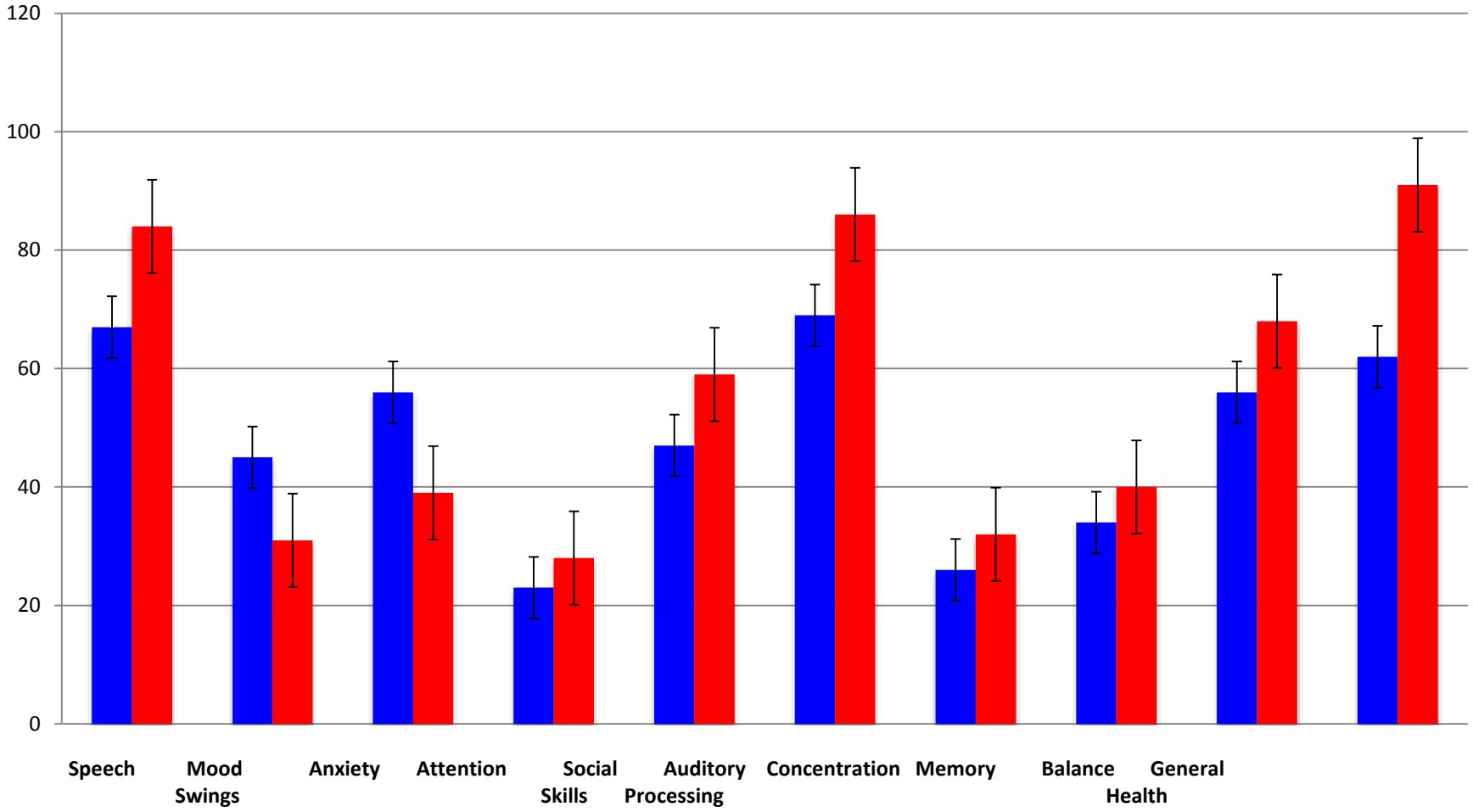
- Autism spectrum disorders (ASD) are pervasive neurodevelopmental disorders that have long been associated with disturbances in communication, social interactions, cognition and affect.
- The ASD are also characterized by repetitive and restricted behaviors. A growing body of evidence is now associating ASD with more complex movement disorders, including ataxia.

Does this treatment work for Children on the Autistic Spectrum ?

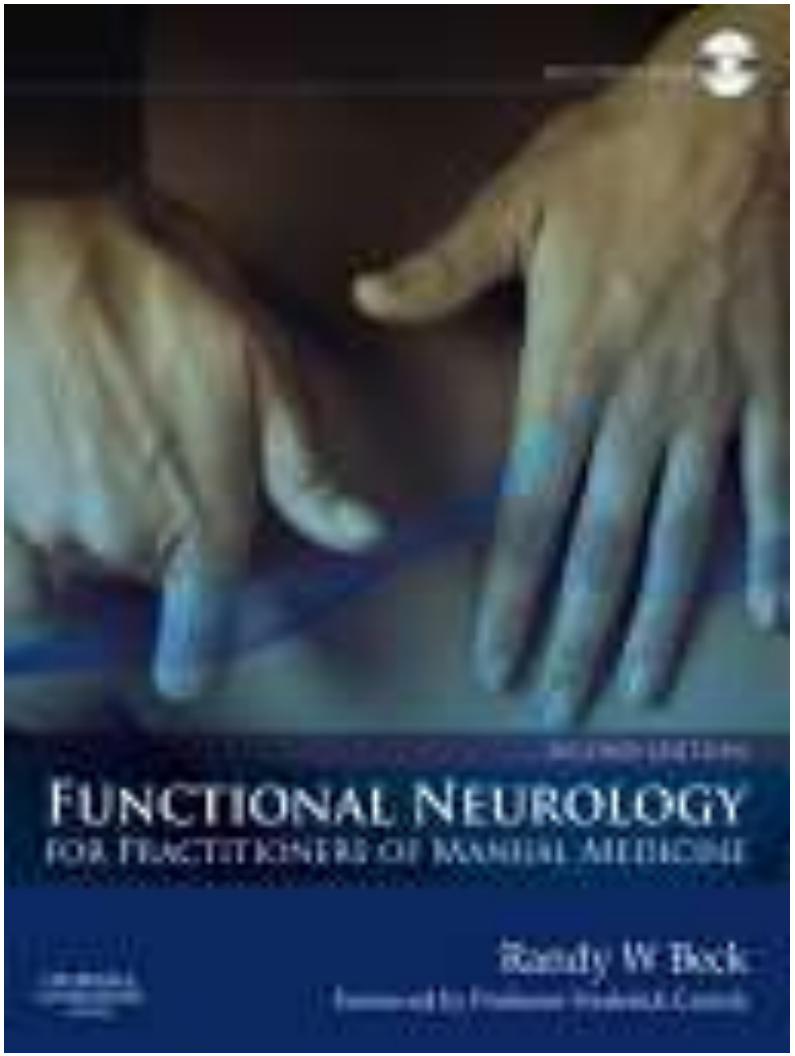
We have compiled a range of statistics retrospectively based on the feedback and comments provided from parents about their child's response to the treatment they have received.

The sample is composed of 36 patients that we have received between 36 and 72 treatment over the last 6 months.

Behavioral Changes in Autistic Children as reported by Parents Feedback over 12 weeks of Care (n=36)



Initial-Blue After 12 weeks-Red



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??? Questions ???