Clinical Electrophysiology as a biomarker diagnostic and treatment in Psychiatric setting

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President of Biofeedback, Neurofeedback, use of QEEG and ERP in Psychiatry Association, Turkey

- Psychiatric disorders interfere with daily-life activities and treated with psychological and pharmacological treatments.
- Psychopharmacology and Psychotherapy for their **high rates of failure to meaningfully improve outcome**s, saying it's time to figure out how to develop "the next generation of interventions."

(Ottowa, 2006; Agency for Healthcare Research and Quality, 2012; Agency for Healthcare Research and Quality, 2011, Surmeli et al., 2011; Surmeli et al., 2012; Surmeli et al., 2016; Surmeli et al., 2009; Paret et al. 2016, Surmeli et al., 2017, Sokhadze, Cannon & Trudeau, 2008)

- A new route map has been drawn for the diagnosis and treatment of psychiatric diseases.
- The National Institute of Mental Health (NIMH)'s call for a more rigorous and evidence-driven approach to mental healthcare. (Kaplan, 2011)
- **It is time that psychiatry moves away from its present focus on medications and takes a new direction that uses other modalities of care evidence-based therapies**.

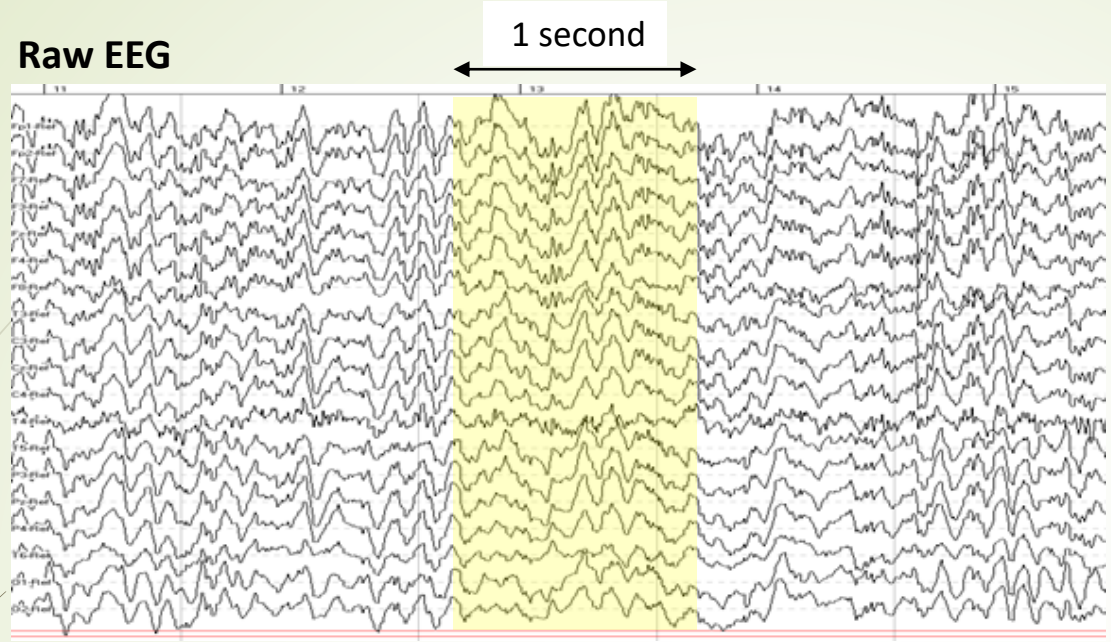
- **Psychiatry and Psychology are the only specialty that doesn't actually look at the organ it treats.**
- Patients deserves more better.
- **We need to devote our self to efficient evidence based diagnosis of disorders and personalized treatments.**
- New methods of treatment are necessary and **Neurofeedback (NF) is one treatment that seems to be effective in psychiatric disorders.**

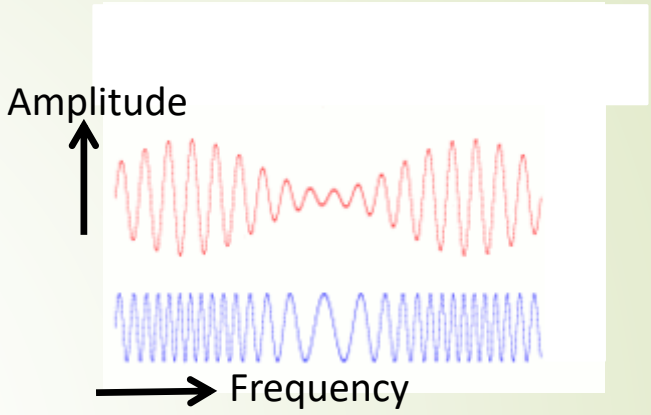
We need new treatment model

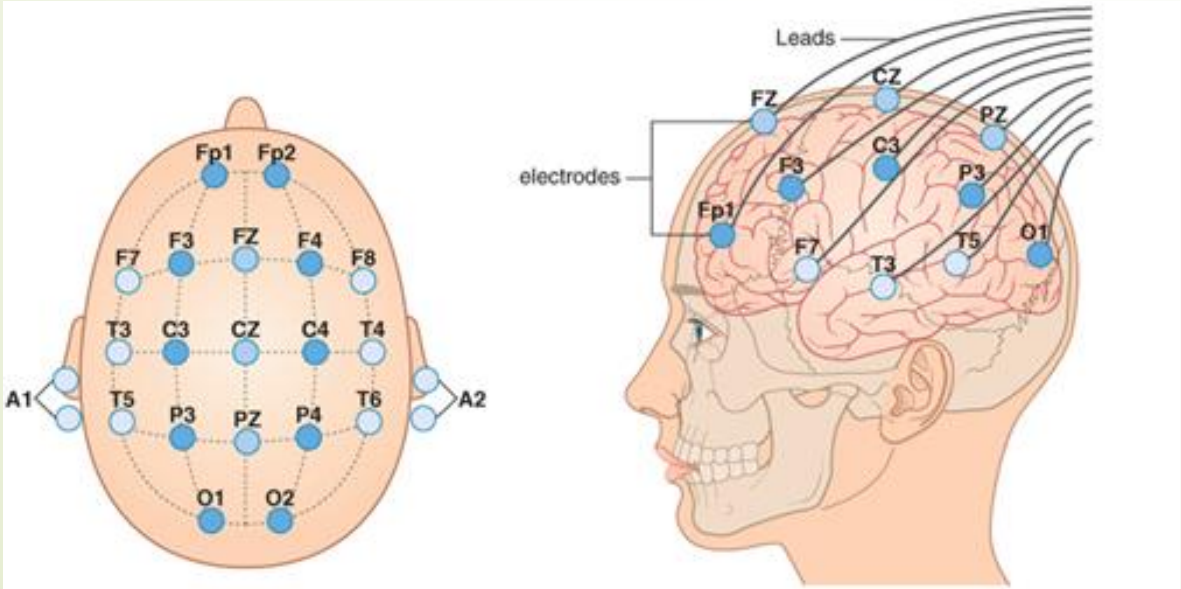
	Disorder	Medication effect
American National Economic Bureau (Currie J, et al.,2014)	ADHD	10 y. Follow up, None
PATS (Preschool ADHD Treatment Study) (Riddle MA., et al., 2013) 3-5 y.o, 207 children,	ADHD	6 y. Follow up, None
Meta analysis and Antidepressant **STAR*D** studies (Kirsch I, et al2002; Pigott, H.E., et al 2010). Meta-analyses reported rates for remission and response were found to be limited as well. (Leichsenring,F et al, 2019)	Depression Depression Anxiety Disorders	Minimum between 37% and 43%
The clinical antipsychotic trials of intervention effectiveness (**CATIE**) NIMH study (Lieberman et al, 2005) Sixty Years of Placebo-Controlled Antipsychotic Drug Trials Meta analysis (Leucht,S et al,2017)	Schizophrenia Acute Schizophrenia	Minimum 23% vs 14% "good"
Electroshock **(ECT)** (Read J.,Bentali R., 2010)	Depression Schizophrenia	Minimum Minimum

- Treatment strategies for **OCD**, most of which **combine medications with psychotherapy**, however display clinical outcomes that are **often unsatisfactory**. (Surmeli et al., 2011; Wang & Xiao, 2015)
- Shekelle et al., (2007) reviewed and found **low strength of evidence for antipsychotics** for combat and noncombat-related **PTSD**.
- Cholinesterase inhibitors can be effective in maintaining cognitive functions in mild to moderate **Alzheimer's Disease**, but they **are less effective for very mild or severe for**ms of the disease and are only **40% to 50% effective**. (Cummings et al., 2002)

Raw EEG

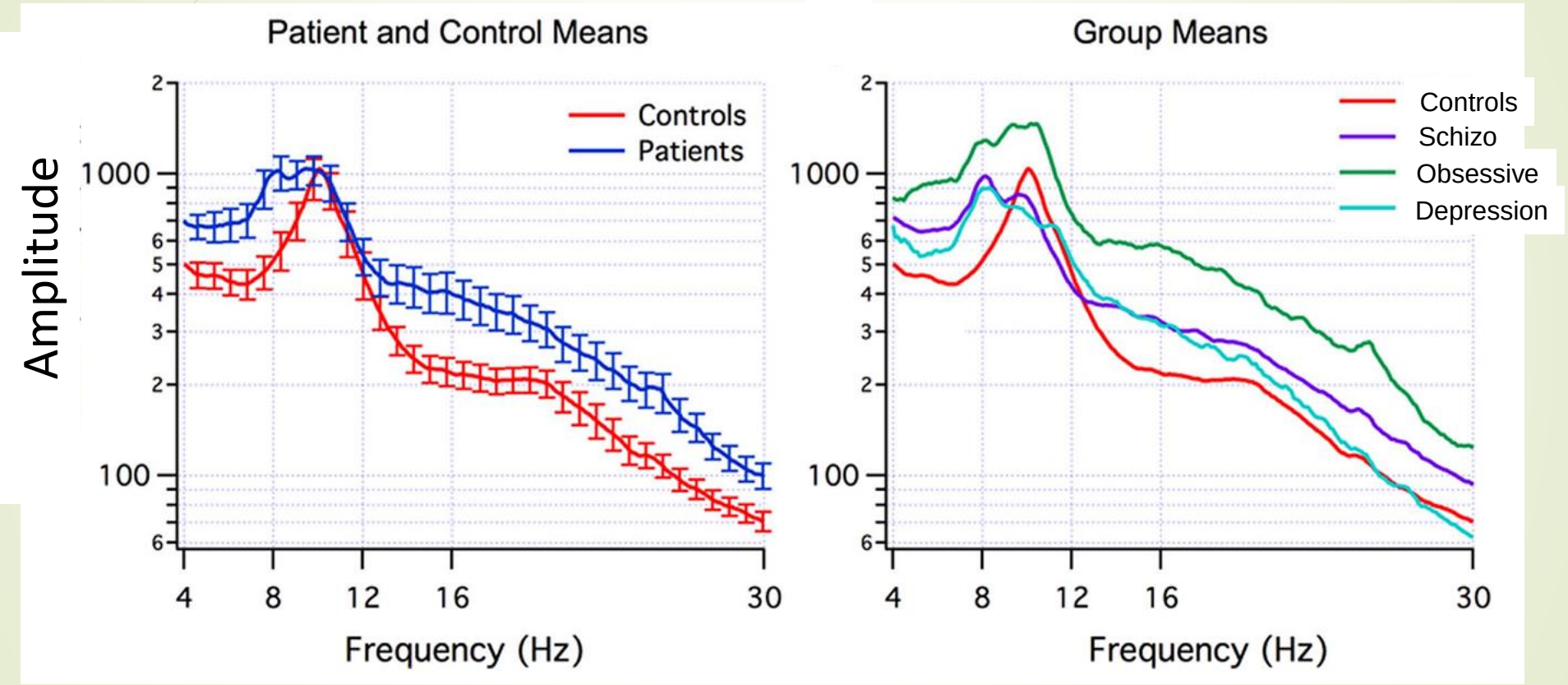






Deployment of surface electrodes on the scalp. *Letters*: C, coronal; F, frontal; Fp, frontopolar; O, occipital; P, parietal; T, temporal; Z, midline. *Numbers*: Odd numbers, left side; even numbers, right side. A1, A2, reference electrode

EEG synchronization (amplitude) is abnormal in psychiatric disorders

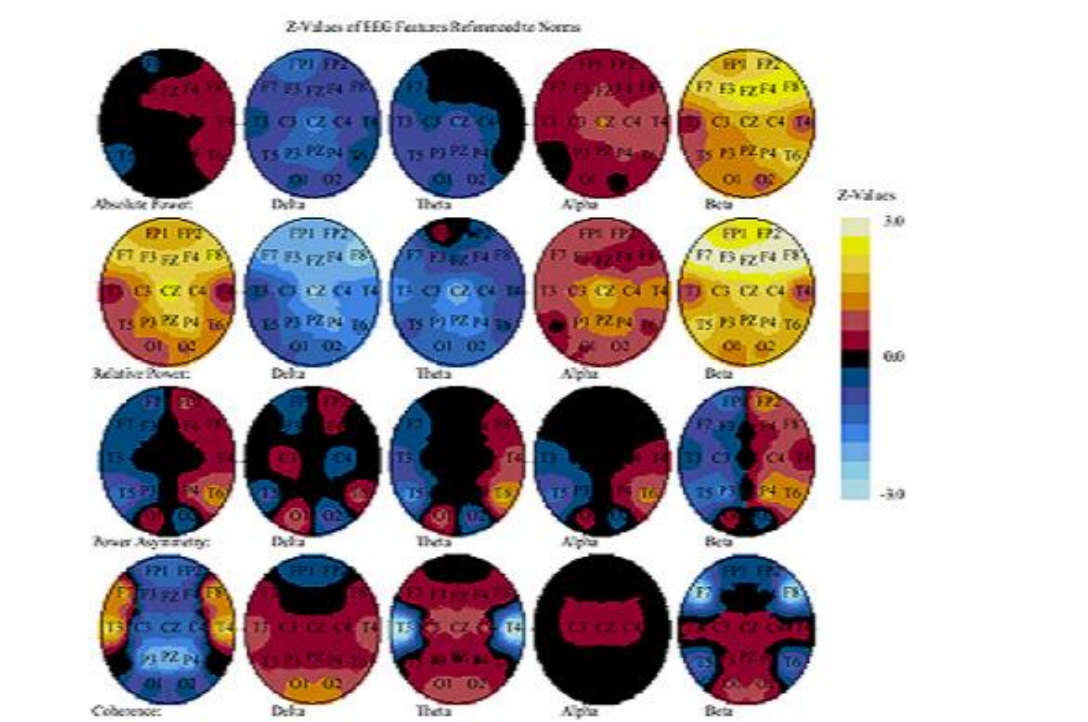


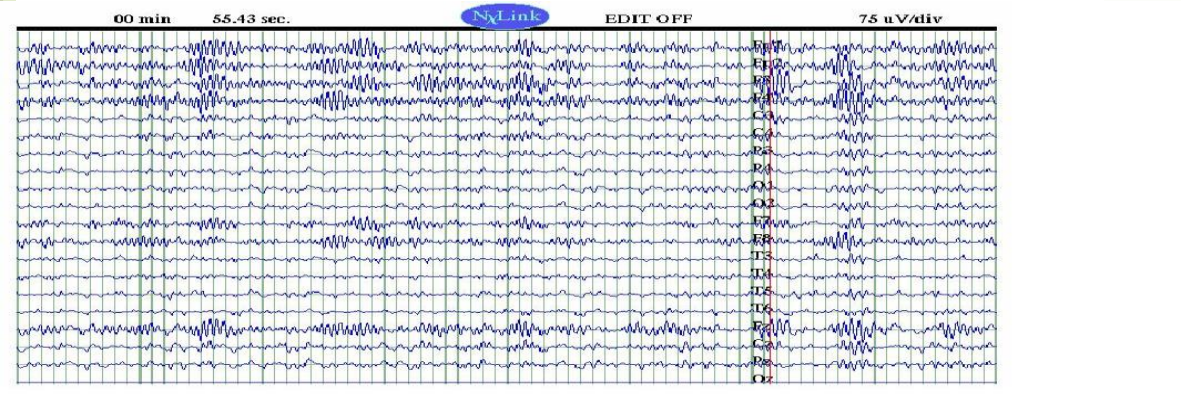
(Schulman et al, Frontiers in Neuroscience 2011)

Reference	Groups [Ns]	Accuracy of Separation [Statistical Method]	Sensitivity/ Specificity [%]
Chabot, Merkin, Wood, Davenport, & Serfontein, (1996)	ADD/ADHD [407] vs Learning Disabled [115], LD vs Normal Control, NC [310]	Training=NCvsADD vs LD =78% Split-half Replication = 70% [Discriminant Function]	**97.0/84.2**
Deslandes et al., (2004)	Dementia [74] vs Depression [51]	Training = 91.2% Jackknife = 90.4% [Discriminant Function]	**91.9/92.2**
Huang et al., (2000)	Alzheimer's disease, AD [38] vs normal controls, NC [24] vs Mild Cognitive Impairment, MCI [31]. MCI who progress, PMCI [14] vs MCI stable, SMCI [17]	AD vs NC = 85% AD vs MCI = 78% PMCI vs SMCI = 87% [no replications] [Discriminant Function]	**87.0/83.0** **87.0/68.0** **79.0/94.0**
Knott, Mahoney, Kennedy, & Evans, (2001)	Unipolar Major Dep [69] vs Normal Controls [23]	Training = 91.3% Jackknife = 91.3% [Discriminant Function]	**Training: 91.3/91.3** **Jackknife: 91.3/91.3**
Knott, Bakish, Lusk, Barkely, & Perugini, (1996)	Panic Disorder [34] vs Normal Controls [19]	75.5% [no replication] [Discriminant Function]	**88.9/61.5**
Lindau et al., (2003)	Frontotemporal Dementia, FTD [19] vs Alzheimer's disease, AD [16] vs normal controls [19]	AD vs Control = 80% FTD vs Control = 79% FTD vs AD = 71% [no replications] [Logistic Regression]	**Not Available**
Struve, Straumanis, & Patrick, (1994)	Chronic marihuana users [18] vs non-user controls [35]	Training = 95% Jackknife = 93.8% [Discriminant Function]	**Training: 100/92.5** **Jackknife: 96.3/92.5**
Thatcher et al., (2001)	Mild Traumatic Brain Injury, TBI [40] vs Severe TBI [43]	MTBI vs STBI = 96.4% [clinical validation] [Discriminant Function]	**95.5/97.4**
Winterer et al., (1998)	**Alcoholic Relapsers [25] vs Abstainers [15]**	**Training = 86.8%** **Test = 85%** **[Artificial Neural Network (ANN)]**	**Training:87.5/92.9** **Test: 88.0/53.3**

The children with ADHD who show increased beta activity ranges from **13% to 20%**

(Clarke, Barry, McCarthy, Selikowitz, Clarke, & Croft, 2003).



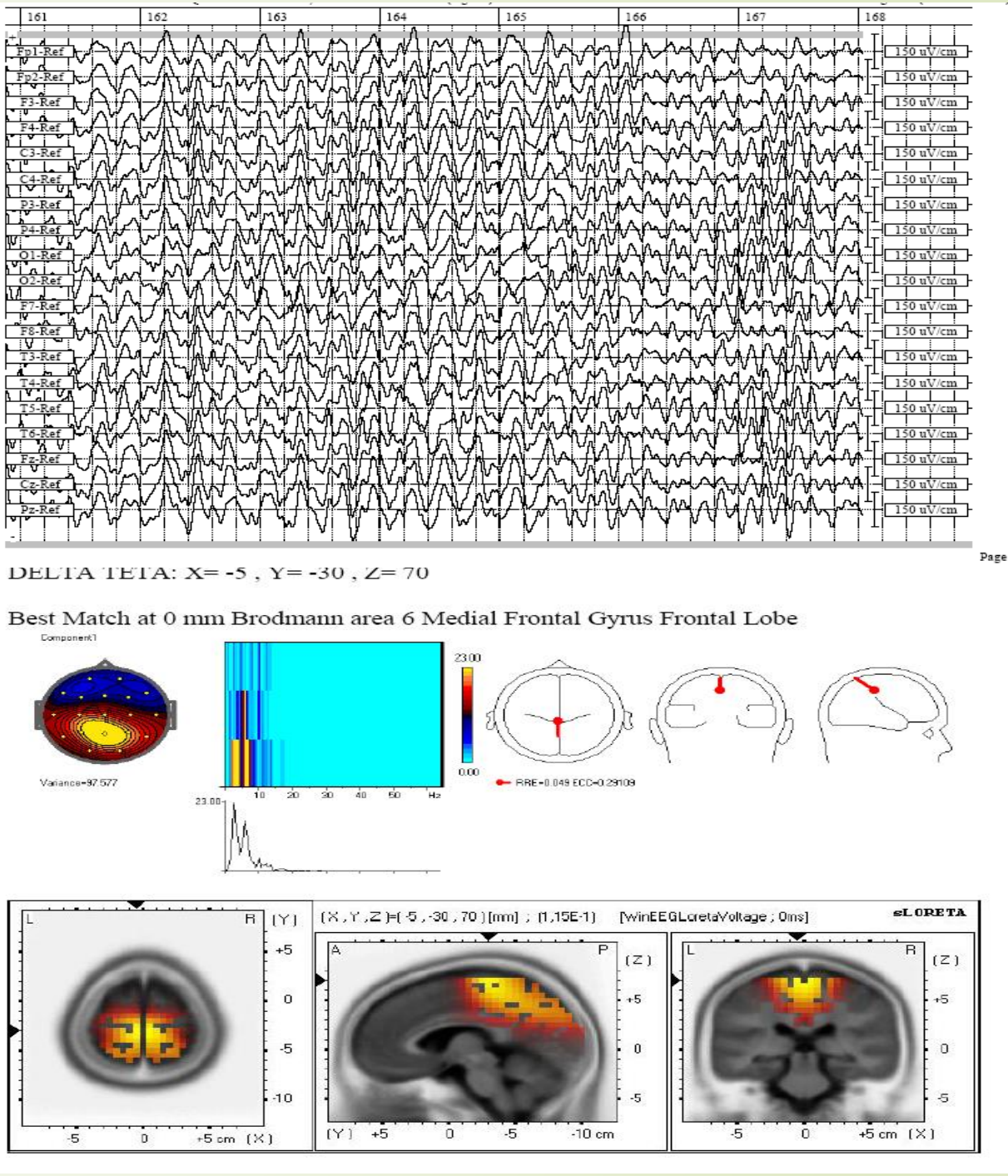


- Behaviorally, this group was similar to other children with ADHD, although the **excess-beta group was more prone to temper tantrums and to be moody.**
- The excess in beta activity was found primarily in the **frontal regions** and may be associated with frontal lobe self-regulation and inhibition control.
- These irritable cortex beta spindles respond well to ion channel blockers, as well as to anticonvulsants or Neurofeedback. (Gunkelman,2014)

Non-Epileptic, ADHD

- **A review of 8 studies of non-epileptic** children with ADHD, found that the prevalence of epileptiform EEGs ranged from **6%** to as high as **53%**, with an average of **23.4%**.
- There is now considerable evidence that **interictal EEG abnormalities** may have **a role in cognitive impairment** and these impairments rarely improve **unless there is a simultaneous improvement in their EEGs**.

  (Binnie, 2003; Holmes & Lenck-Santini, 2006)



Epilepsy


130
131
132
133
134
135
136
137
Fp1-Av
Fp2-Av
F3-Av
F4-Av
C3-Av
C4-Av
P3-Av
P4-Av
O1-Av
O2-Av
F7-Av
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T3-Av
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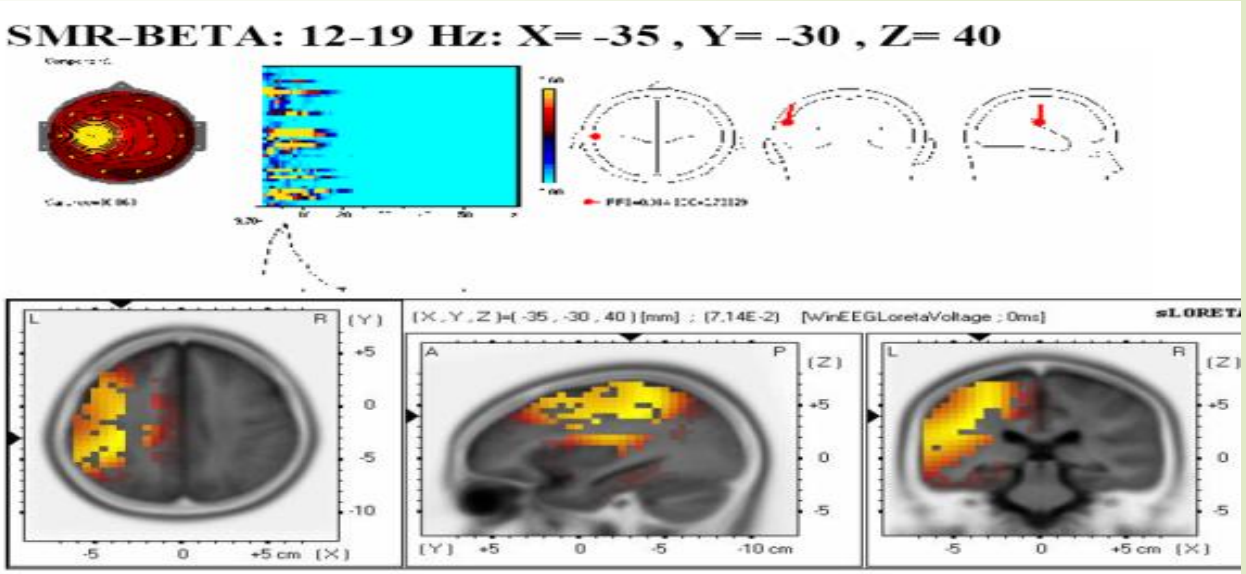
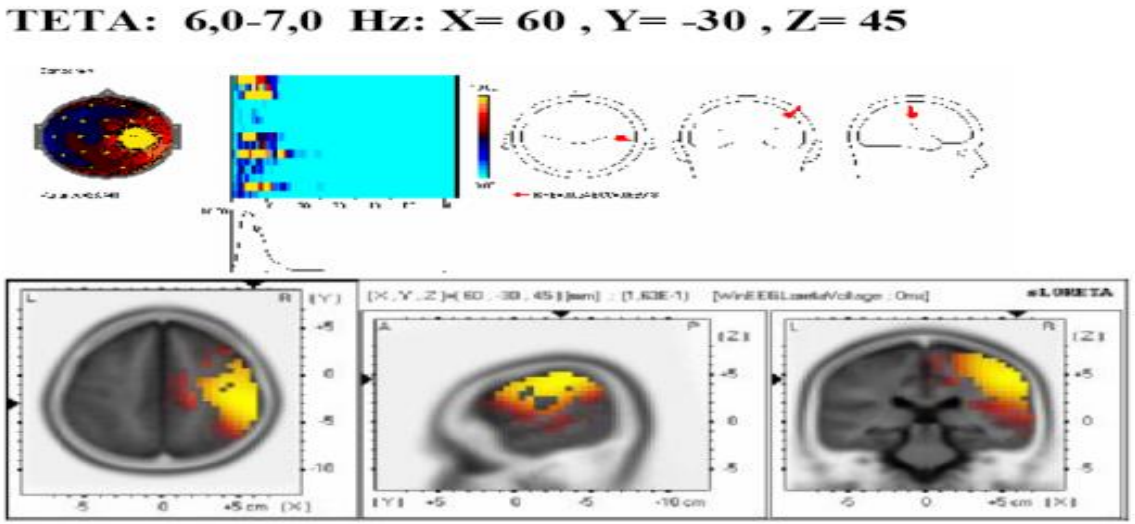
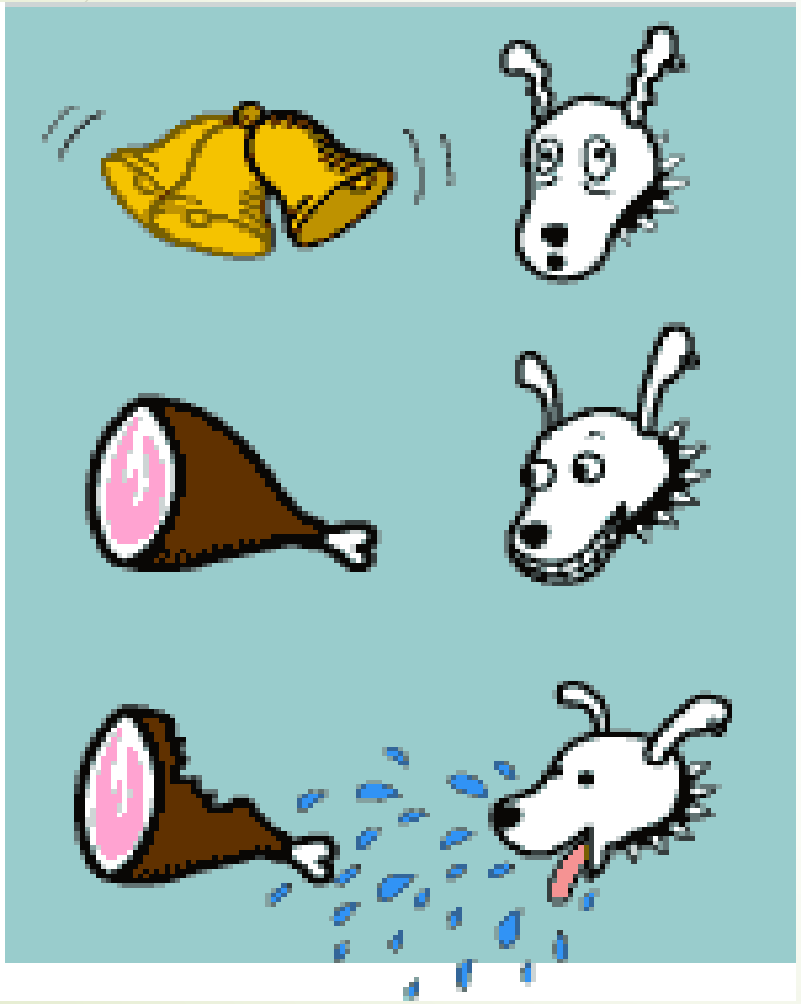
T5-Av
T6-Av
Fz-Av
Cz-Av
Pz-Av


SMR-BETA: 12-19 Hz: X= -35 , Y= -30 , Z= 40
[X,Y,Z]=(-35,-30,40) [mm] ; (7.14E-2) [WinEEGLoretaVoltage ; 0ms]
sLORETA

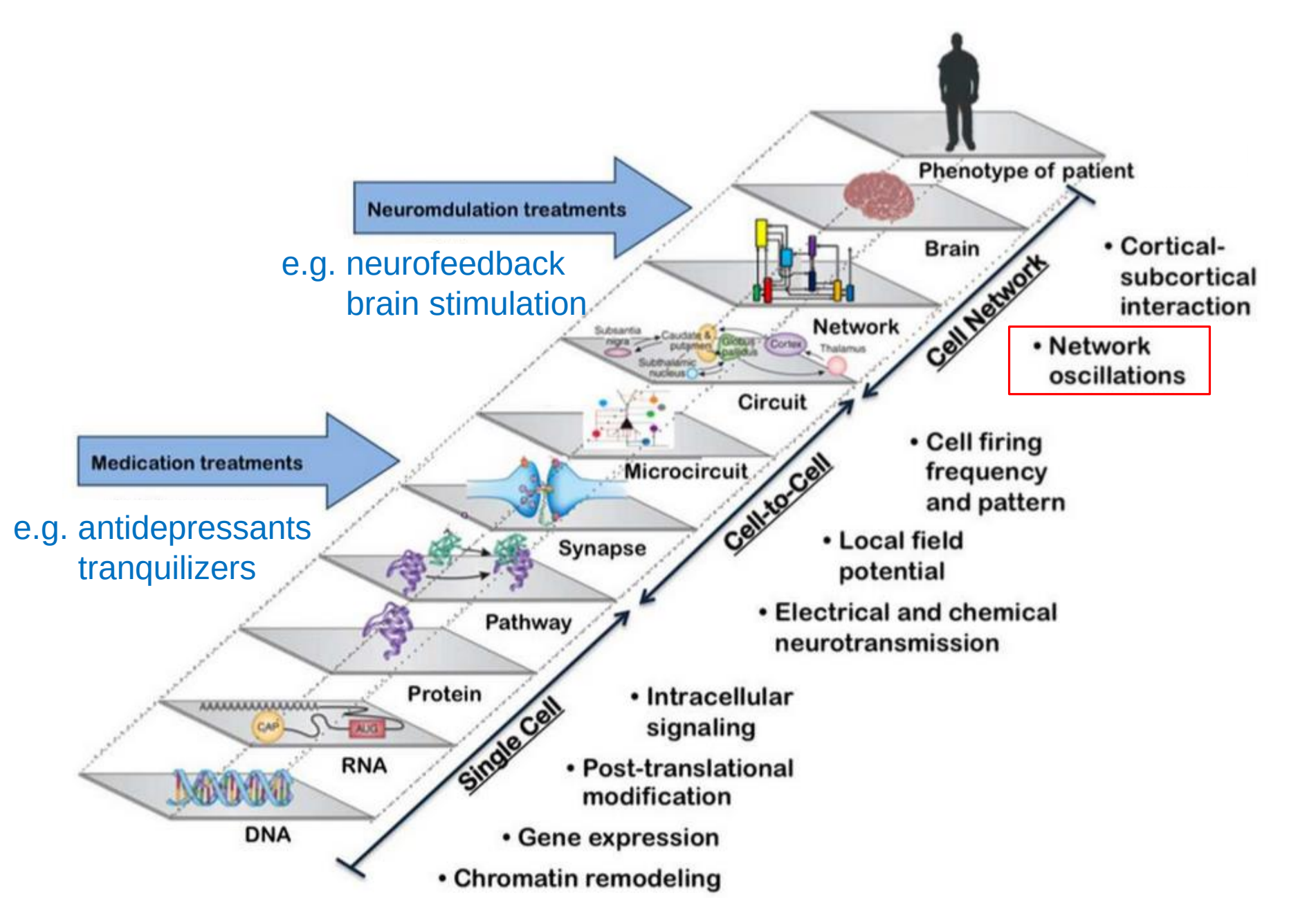

TETA: 6,0-7,0 Hz: X= 60 , Y= -30 , Z= 45
sLORETA

2 Nobel Prize for Operant Conditioning

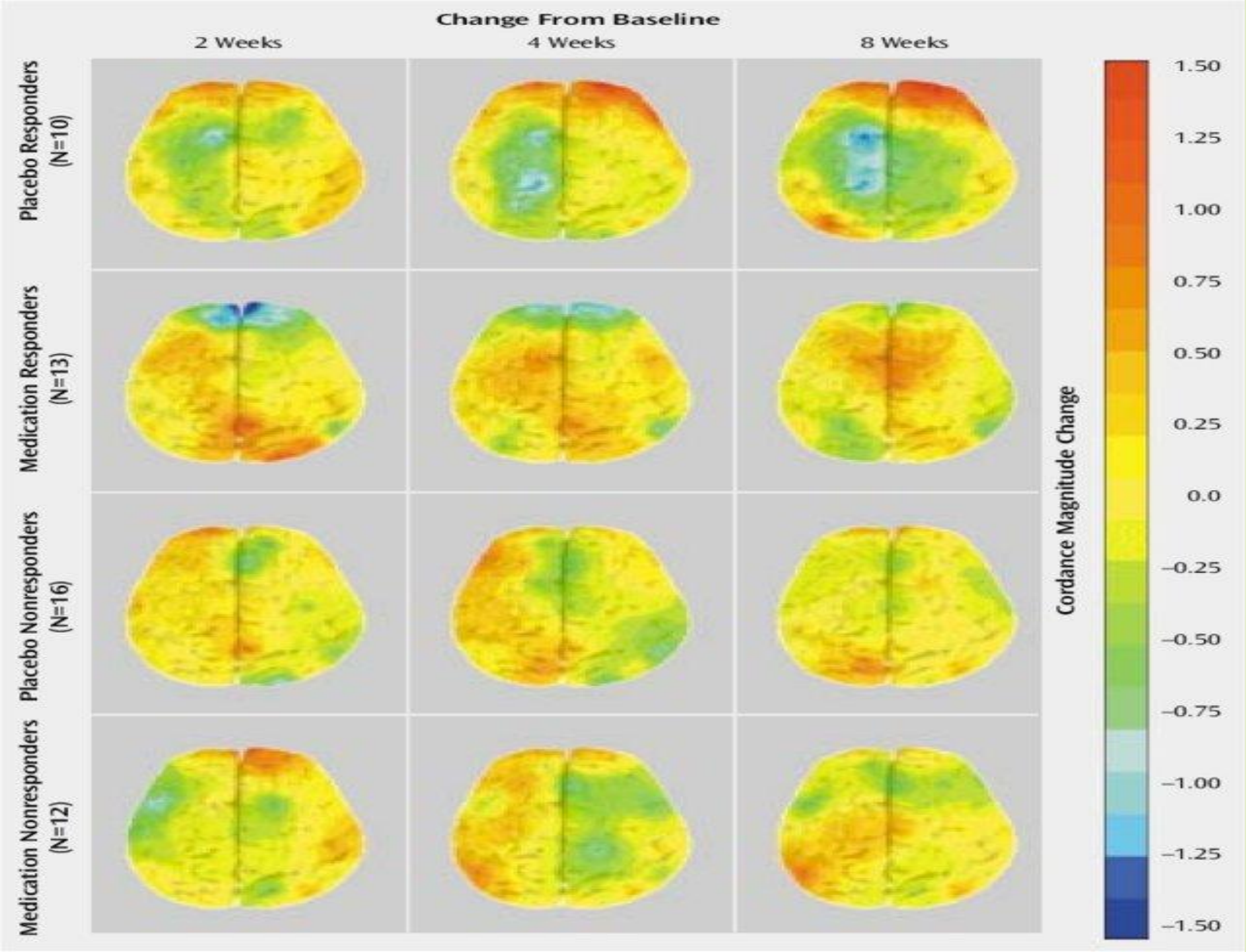


- Pavlov won Nobel prize in 1905,
- Ringing the bell increase the salivation of dog.
- Prof. Dr. Eric Kandel won a Nobel Prize in 2000 for showing that **synaptic mechanisms of classical conditioning and operant conditioning** (including RNA/DNA mechanisms) are **universal** throughout the animal kingdom, including humans.

- The evolution of neurofeedback was made possible by an array of pioneers that laid the bedrock for the fundamental principles and quantitative technology.
- Starting with Pavlov's nobel prize awarded work on operant conditioning of his dog in 1905, the application of this principle was carried on to cats by Barry Sterman and to medical students Joe Kamiya.
- B.F. Skinner who extensively studied operant conditioning argued that instrumental or operant learning involves rewards that are reinforcers of stimulus-response (S-R) links that **do not require mental processes** such as **intention, representation of a goal, or consciousness** (Skinner, 1953).
- Yet, without the discovery of electroencephalography (EEG), subsequent quantified EEG through Fourier analysis, and the examination of maturation using EEG by Hans Berger, that the course for neurofeedback's development would not be set.
- In 1934, E. D. Adrian and B. H. C. Matthews recorded the first EEG-feedback experiment, yet for a different purpose than it is used today.



Leuchter et al 2015


Change From Baseline
2 Weeks
4 Weeks
8 Weeks
Placebo Responders (N=10)
Medication Responders (N=13)
Placebo Nonresponders (N=16)
Medication Nonresponders (N=12)
Cordance Magnitude Change
1.50
1.25
1.00
0.75
0.50
0.25
0.0
−0.25
−0.50
−0.75
−1.00
−1.25
−1.50

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Tuning pathological brain oscillations with neurofeedback: a systems neuroscience framework

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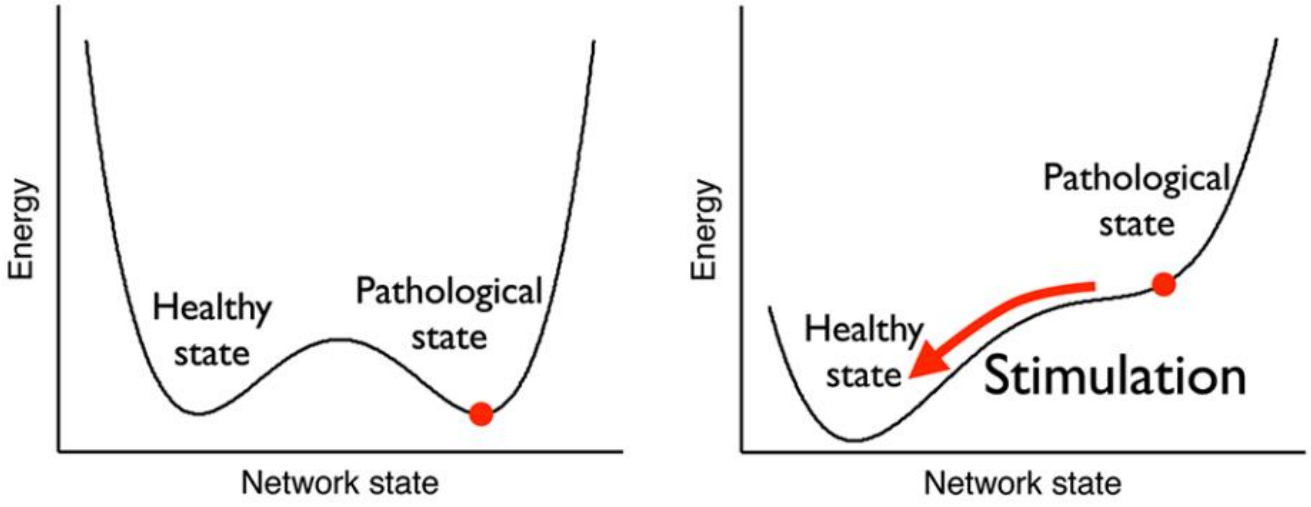


NEUROFEEDBACK

- Neurofeedback is a training based on operant learning strategies.
- The simultaneous and contingent (conditioned) feedback of **neurophysiological signals** is provided with the aim to learn to control the processes underlying these signals and thereby **enhance self-regulation**.
- Changes in **cognitive–emotional–behavioral** or physiological activity in the desired direction are reinforced by **auditory and/or visual feedback**.
- Feedback is usually presented in the form of simple computer games in which people can earn points (e.g., by moving objects on the screen).

NEUROFEEDBACK

- Neurofeedback (NF) is not a one size fits all type of treatment.
- Each treatment protocol must be personalized to each patient, and regularly monitored and adjusted for optimum treatment effect.
- With the growing importance of **personalized medicine**, these types of treatments may become more common in the future.

- The QEEG guided NF fits the description of **personalized** since the NF protocol is tailored to the individual QEEG results of the patient.
- EEG Neuroimaging swLORETA navigator (**the ability to image deep and surface sources)** or **fMRI NF** can be used for personalized treatment.
- 3-Dimensional NeuroImaging of Functional Brain Networks

  - sLORETA of Brodmann Areas & sLORETA of Networks in Real-Time

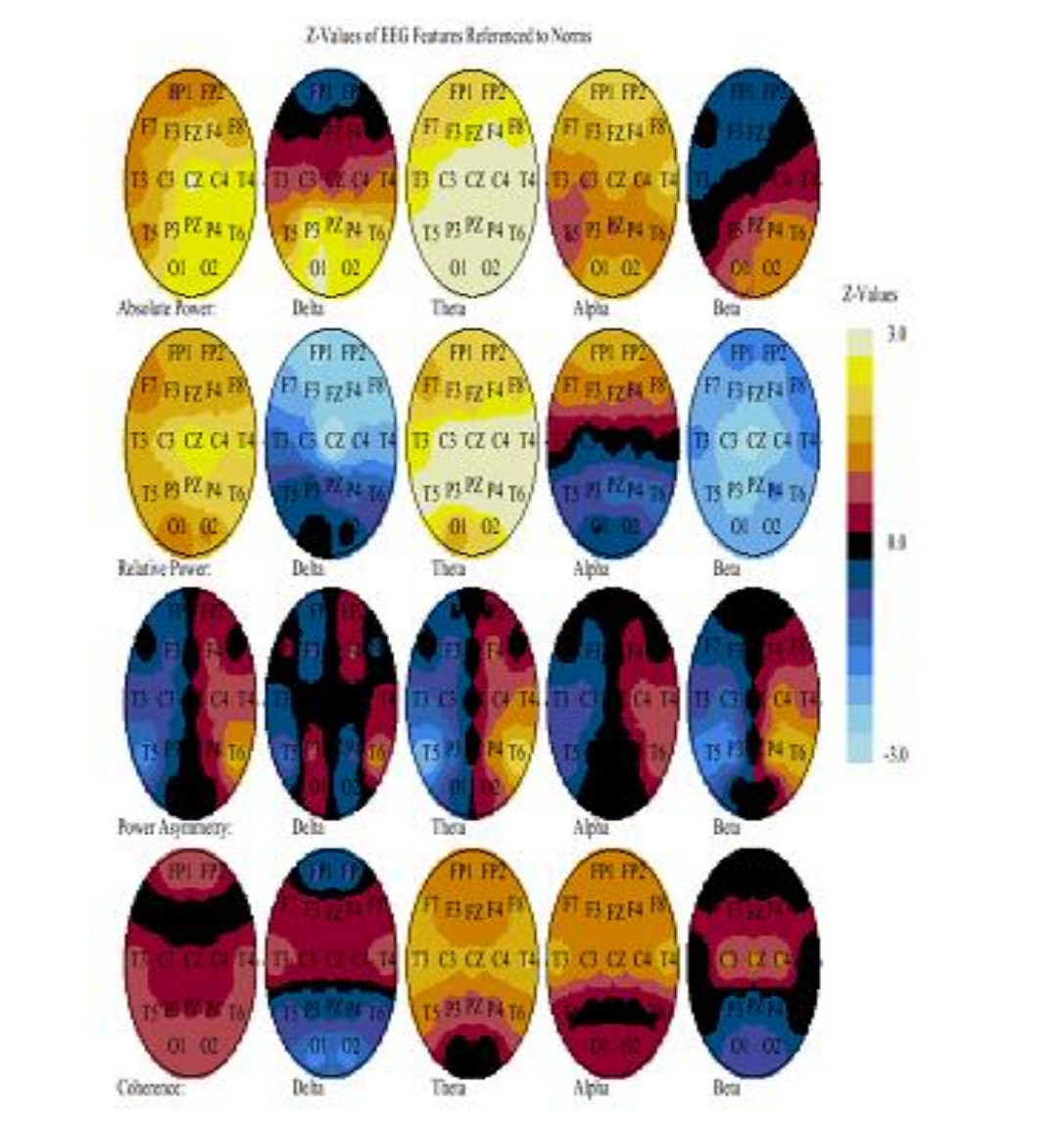
  -Live Z scores of nodes and connections between nodes as measured by sLORETA Coherence and

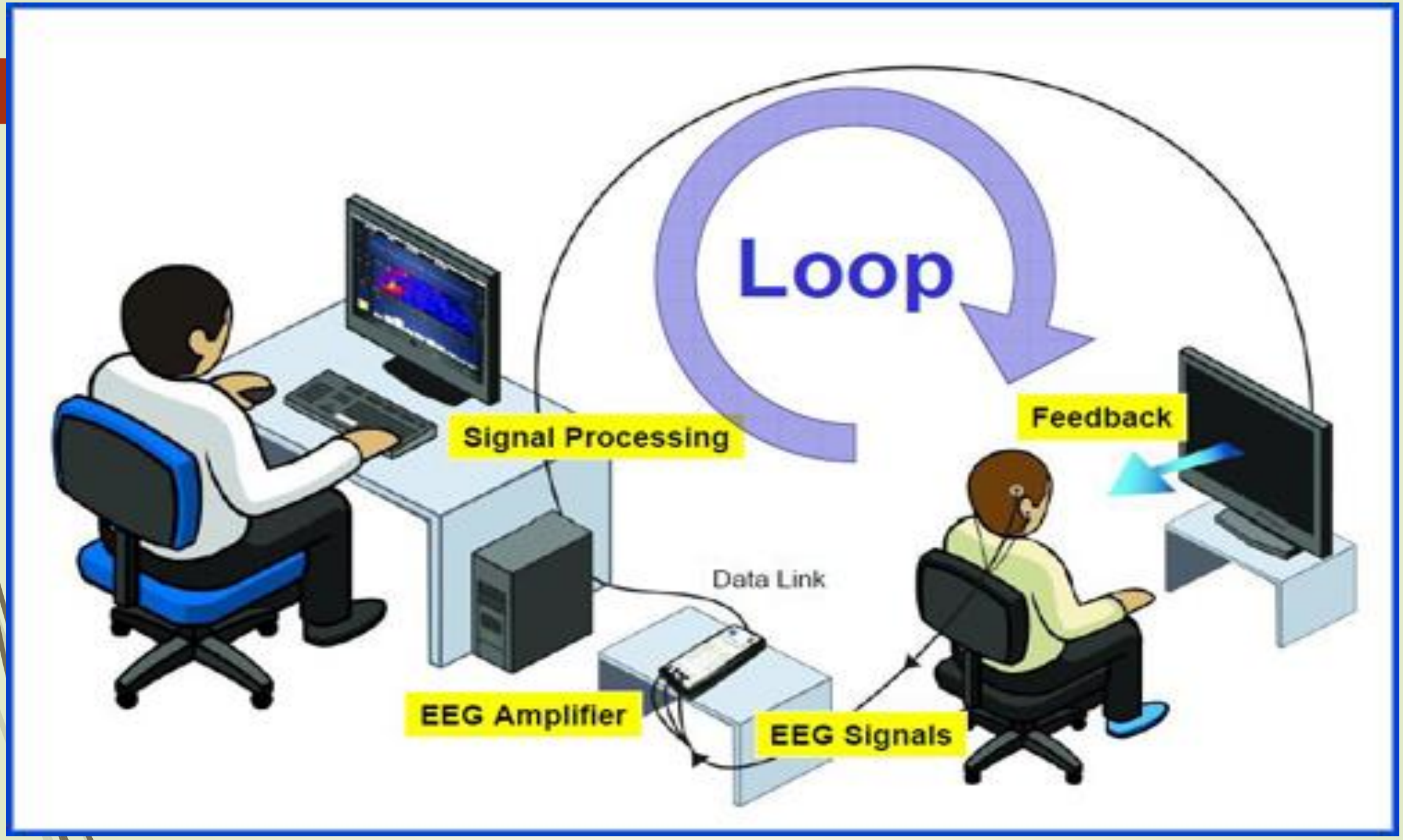
  sLORETA Phase Differences.

- In neurometric qEEG analysis, variables are Z scores (distance from the norm in standard deviation (SD) units.
- A general rule is to link the patient's symptoms to deviant Z scores located in regions of the scalp related to functional specialization in the brain.
- The rationale is that the participants who normalize their qEEG Z scores would benefit the most. (Thatcher,1998)

ADHD, QEEG, Neurometrics

- Children with ADHD typically have increased EEG slow wave activity, primarily in the **theta** band, compared to normal children (Mann, Lubar, Zimmerman, Miller, & Muenchen, 1992).
- Increased relative **delta** activity in **posterior regions** is also common in children with ADHD. (Matousek, Rasmussen, & Gilberg, 1984).




Loop
Signal Processing
Feedback
Data Link
EEG Amplifier
EEG Signals


JVC
SCORE
ROUND
13
0
DELL

Evidence of Brain Plasticity

- There are some studies that show **the effect of NF on brain plasticity** with evidence that NF could be used in many diseases of the brain
- such as controlling the person's **pain** in the rostral Anterior Cingulate Cortex (ACC) with fMRI NF (**DeCharms et al., 2005**) ;
- an **increase in the gray matter vo**lume and an increase in cable thickness was observed in the areas of white matter (**Ghaziri et al., 2013**) with fMRI NF;
- It is impossible for people to control the frontal lobe of the brain but the people could **learn to control the anterior lobe with fMRI NF** (Malach et al. 2013), and the effect was permanent 24 hours after that recording.

- The functional connectivity of distinct **salience network** (dorsal anterior cingulate focus) was plastically altered **after a 30-min session of voluntary reduction of alpha NF** (not with a sham feedback condition) during the performance of an attentional task in healthy participants. (Ros, 2013)
- This network is involved in including
- **ADHD, addiction disorders, MDD, schizophrenia, fronto-temporal dementia, and PTSD.**
- Thus, finding ways to alter network connectivity may be a valuable tool in the treatment of PTSD.

- Engelbregt et al. (2016) randomly assigned subjects to active or **sham NF**, and the real NF group's **increased frontal beta activity** was accompanied by altered cognitive performance which was **maintained 3 years post training**.
- Ramot et al. (2016) demonstrated that **a reward-control loop** can cause connectivity changes even **without the person's knowledge and awareness**.
- Those control loops are the **true power of NF**.
- NF can be considered as a way of teaching the brain to control cortical function by creating new feedback pathways, or forming new reward-control loops that are associated with various pathologies, **which might be difficult to control via a definite task or strategy**, and may have potential uses with severe clinical disorders and/or when there is difficulty in not ensuring **conscious awareness**.

Mental disorders result from brain dysregulation

- neurological under-arousal (e.g. depression),
- neurological over-arousal (e.g. anxiety) or
- instable-arousal (e.g. PTSD),

in that patients have problems in **intentionally controlling neural functioning**. (Russell-Chapin, 2011)

ADHD

- NF review and/or meta-analysis studies of ADHD in children showed **medium impact sizes** for general indication diminishment (Lofthouse, Arnold, Hersch, Hurt, DeBeus, 2011; Micoulaud- Franchi et al., 2014), and medium (Micoulaud-Franchi et al., 2014) **to large** (Arns, de Ridder, Streh, Breteler & Coenen, 2009) impact sizes on obliviousness.
- Regarding nonpharmacological treatments for ADHD, a meta-analytic review found that neurofeedback is the most effective treatment based on the average weighted effect size comparing to other psychological interventions such as parent training, school based, self-monitoring, multimodal psychosocial, working memory training, behavior modification. (Hodgson, Hutchinson & Denson, 2014)
- A **2018 meta-analysis result from 10 randomized, controlled tri**als of more than 500 participants, consisting mostly of children ages 8-12, found that neurofeedback significantly reduced inattention, hyperactivity, and impulsivity for **2 to 12 months after treatment ended for children with ADHD.** Neurofeedback drives enduring ADHD symptom improvement. (Van Doren et al., 2018)

- Meta analysis of NF studies in Epilepsy showed significant improvement (Tan, et al., 2009).
- In a controlled comparison study in children with epilepsy who had an IQ less than 80, the self-regulation of Slow cortical potentials showed **a 7 point increase in IQ scores** of the group (Strehl et al,2011) and in a randomized control study in children with LD NF was "significant in improving **Full Scale and Verbal IQ**"(Fernández et al, 2007)
- In 3 randomized placebo control studies conducted in children with learning disabilities, NF showed **a significant increase in IQ scores**. (Fernández et al, 2003; Becerra et al, 2006; Fernández et al, 2007)
- **A weighted average** (weighted by the number of subjects) of **controlled studies using NF** in children (**6 studies with a total N of 58**) shows an **increase** of **6.9 IQ points** (CI: 5.7 – 8.1) after NF, whereas the normal **controls** show an increase of **only 0.9 IQ points** (CI: 0.0 – 1.9)

(Fernández et al, 2003; Becerra et al, 2006; Fernández et al, 2007; Orlando P, Rivera R, 2004; Leins et al, 2007; Strehl et al, 2011; Mazzone et all, 2011)

Reference		DISORDER	
Choi et al., (2011),	R placebo controlled asymmetry NF training	Depression	**Depression improved**
Linden et al. (2012)	Controlled NF upregulate brain areas involved in the generation of positive emotions (such as the **ventrolateral prefrontal cortex (VLPFC) and insula** during **four NF.**	Depression	**17-item HAM-D, improved significantly.**
Yuan et al., 2014	rtfMRI-nf training of the amygdala during recall of positive autobiographical memories (AMs) and matched healthy subjects	Depression (in unmedicated)	**larger decreases of depression severity associated with larger increases of amygdala connectivity**
Young, Zotev, Phillips et al (2014); Zotev et al. 2016	rtfMRI-nf left amygdala (**experimental group**) or the horizontal segment of the intraparietal sulcus (**control group**)	Depression (in unmedicated)	**experimental group had increased activity compared to the control group in left superior temporal gyrus and temporal polar cortex, and right thalamus resulting in improved mood.**
Young, Siegle, Zotev et al's (2017)	**rtfMRI-nf a double-blind, R Placebo-controlled,** two sessions either from the **amygdala** or from a **parietal region** not involved in emotional processing **(control)**	**Depression (in unmedicated)**	**significantly decreased depressive symptoms**

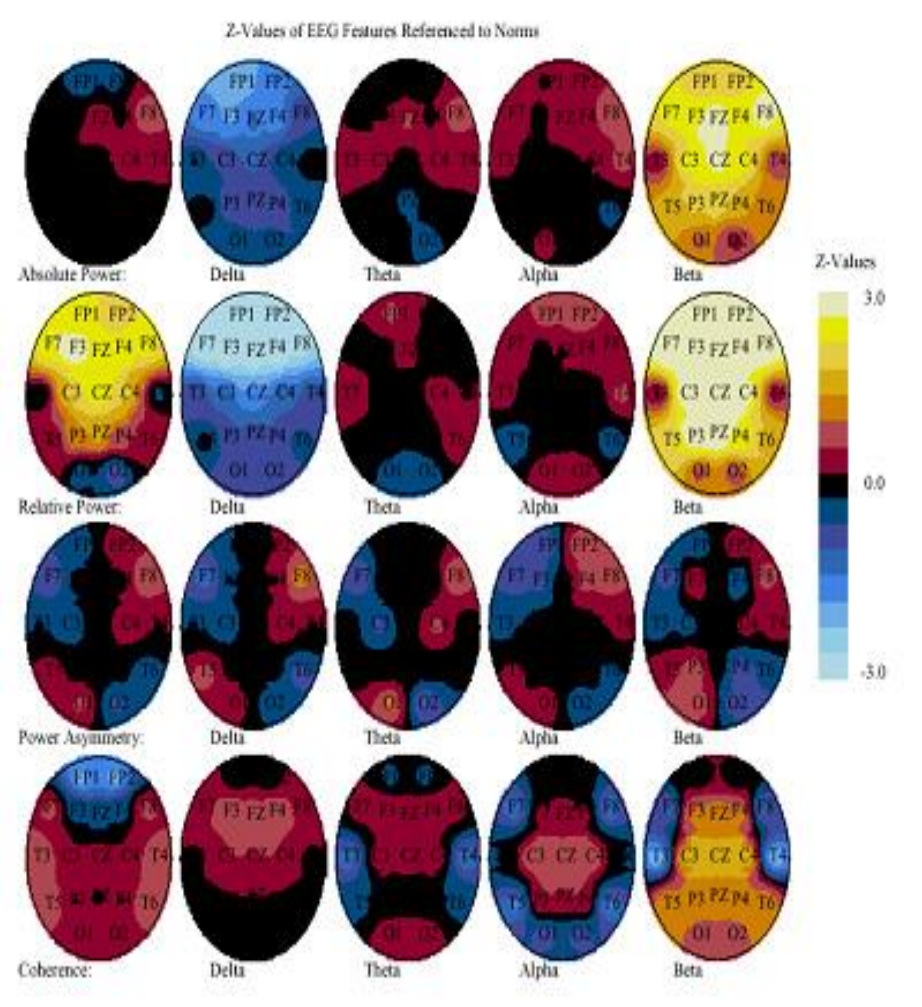
Peniston & Kulkosky, 1991; Peniston, Marrinan, Deming, Kulkosky, 1993	Controlled alpha/theta NF	PTSD chronic combat-related	NF more efficacious modality in the treatment of PTSD and prevention of relapse for 26 and 30 months follow up
Walker (2009)	Compared a QEEG guided NF with the control group	PTSD with anxiety	A significant reduction of anxiety in the NF group.
Gapen et al. (2016)	RCT NF	PTSD with multiply-traumatised chronic treatment-resistant patients	significantly reduced PTSD symptoms
Van der Kolk et al. (2016)	RCT, waitlist (TAU) Brain/Computer Interaction (BCI) NF	PTSD chronic	significant PTSD symptom improvement as well as in affect regulation capacities

Rastegar, Dolatshahi & Rezaei Dogahe (2016)	**Controlled alpha-theta NF**	**PTSD** **inpatient veterans**	**improved sustained attention**
Ros et al. (2017)	**sham controlled** randomized NF	PTSD	**significantly decreased arousal in the PTSD group**
Nicholson et al. (2016)	alpha desynchronization NF	PTSD with childhood sexual and/or physical abuse	**shift in amygdala complex connectivity was associated with reduced arousal and was negatively correlated to PTSD symptom severity.**
Nicholson et al. (2017)	**r-fMRI NF**	**PTSD**	**Increased activation of prefrontal cortex (PFC) negatively correlated with dissociative sxs**

- While the results of these studies are encouraging and suggest the clinical potential of amygdala rtfMRI-nf in alleviating symptoms of major depressive disorder, larger studies are warranted to confirm its efficacy.
- In the effectiveness of NF as a treatment for PTSD. The eleven studies examined used a variety of different NF techniques but found evidence to support NF as a viable treatment for PTSD symptoms such as anxiety, depression and hyperactivity. Some studies also showed reduced rates of substance abuse, relapse, and need for medication. (Trivendi,2018)

Decreasing Beta after NF in Anxiety Disorders

PRE



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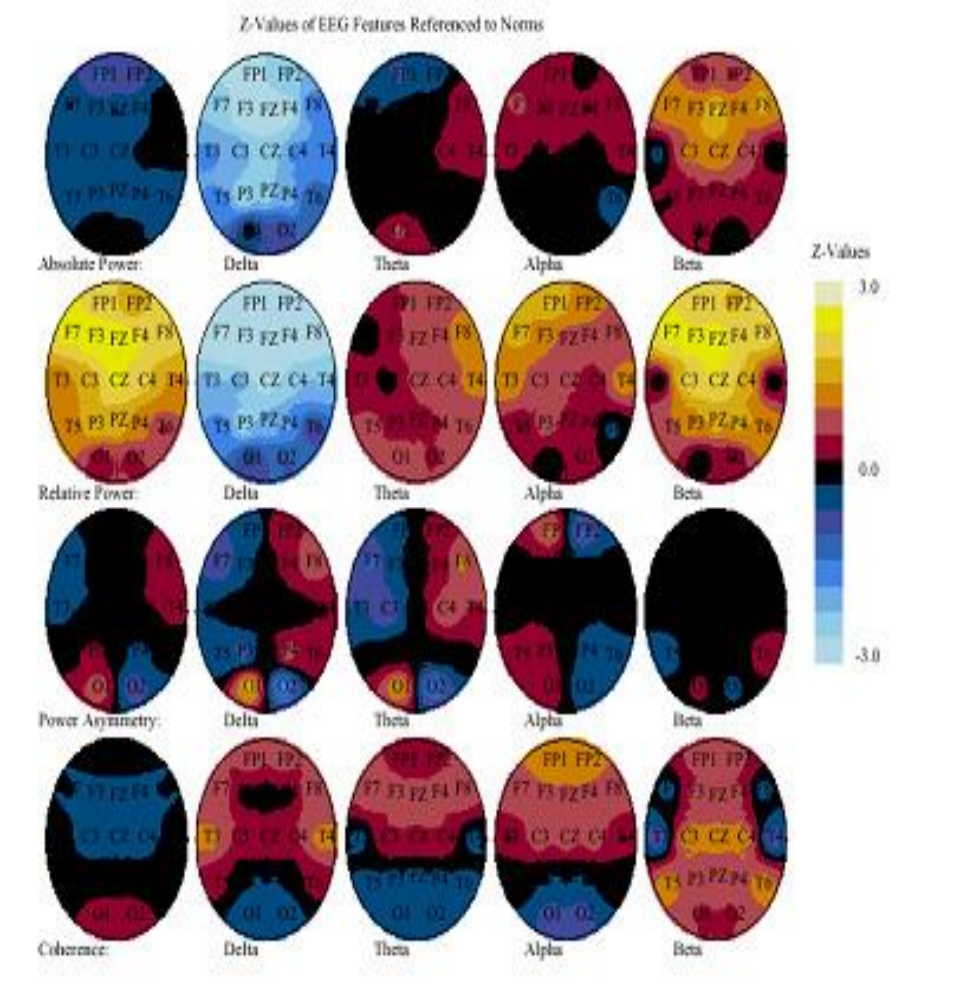
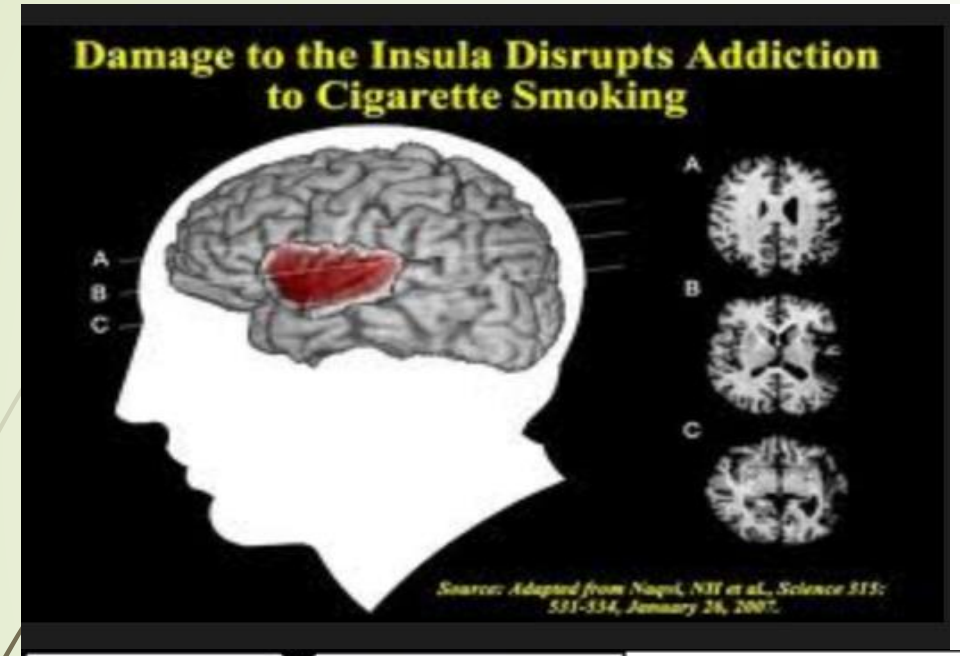


Raymond, Varney, Gruzelier, 2005	RCT alpha/theta NF training or a mock, noncontingent feedback (control)	Anxiety	Improvements in feeling energetic, confident, composed, agreeable and elevated in mood.
Sandhu, Paul, Agnihotri (2007)	**randomly** assigned to three groups: Group I received EMG BF, Group II received alpha NF, Group III served as the control group.	GAD (n:45)	Both Biofeedback trainings are efficacious in the treatment of GAD.
Anna Zilverstand, Sorger, Sarkheil & Goebel (2015)	**single-blind, randomised controlled** NF	Spider phobia	lower levels of anxiety fear demonstrated with a reduction in activation levels in the **insula (associated with emotion processing and regulation)** by cognitive reappraisal and associated with **long-term anxiety reduction.**

Seyed Hosseini, Fathi-Ashtiani,Rabiei,Noohi & Fajrak (2016)	RCT NF	GAD (in military staf)	significant reduction in GAD symptom severity and significant effect size observed in among NF training.
Mennella, Patron & Palomba, 2017	**RCT NF** study of EEG frontal alpha asymmetry group	**GAD**	increase in alpha asymmetry driven by higher alpha at the **right** site as well as a coherent reduction in both negative affect and anxiety symptoms from pre-to post-training.
Yan et al. (2017)	**RCT increase range of alpha band**	**PANIC DISORDER**	NF significantly improved abnormal anxiety in crowded places and public places of panic disorder patients.

Insula/Anterior Cingulate

Schizophrenia,Obsessive Compulsive Disorder/Cigarette addiction (Surmeli et al, 2011, 2012,2014)



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Imaging of thalamocortical dysrhythmia in neuropsychiatry

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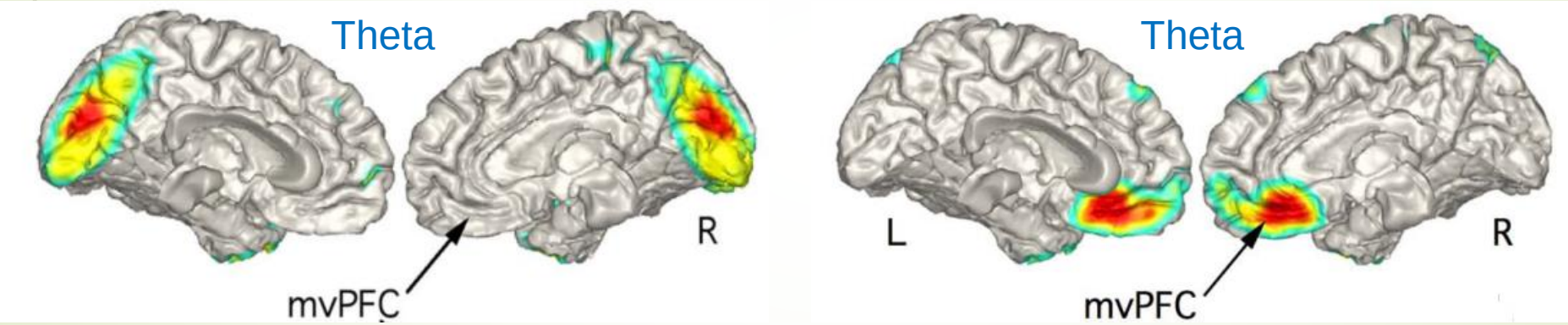
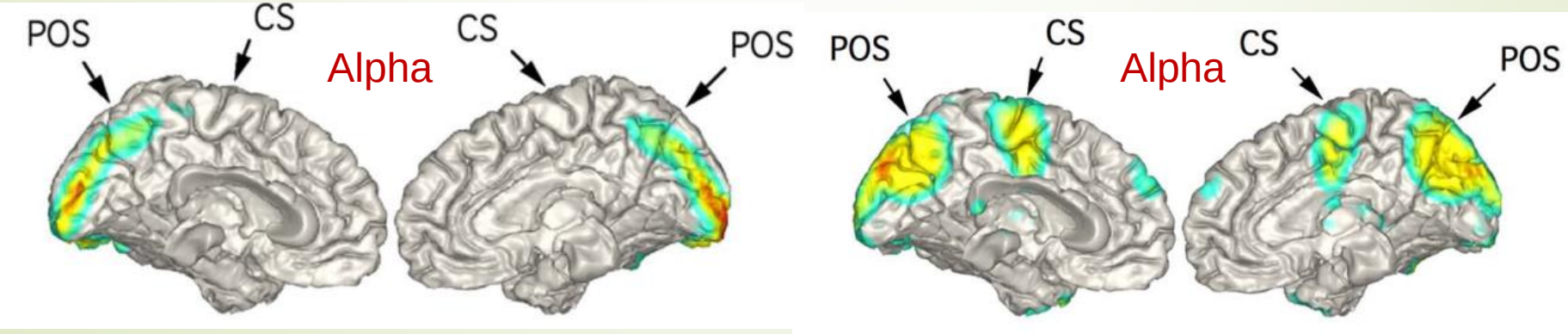
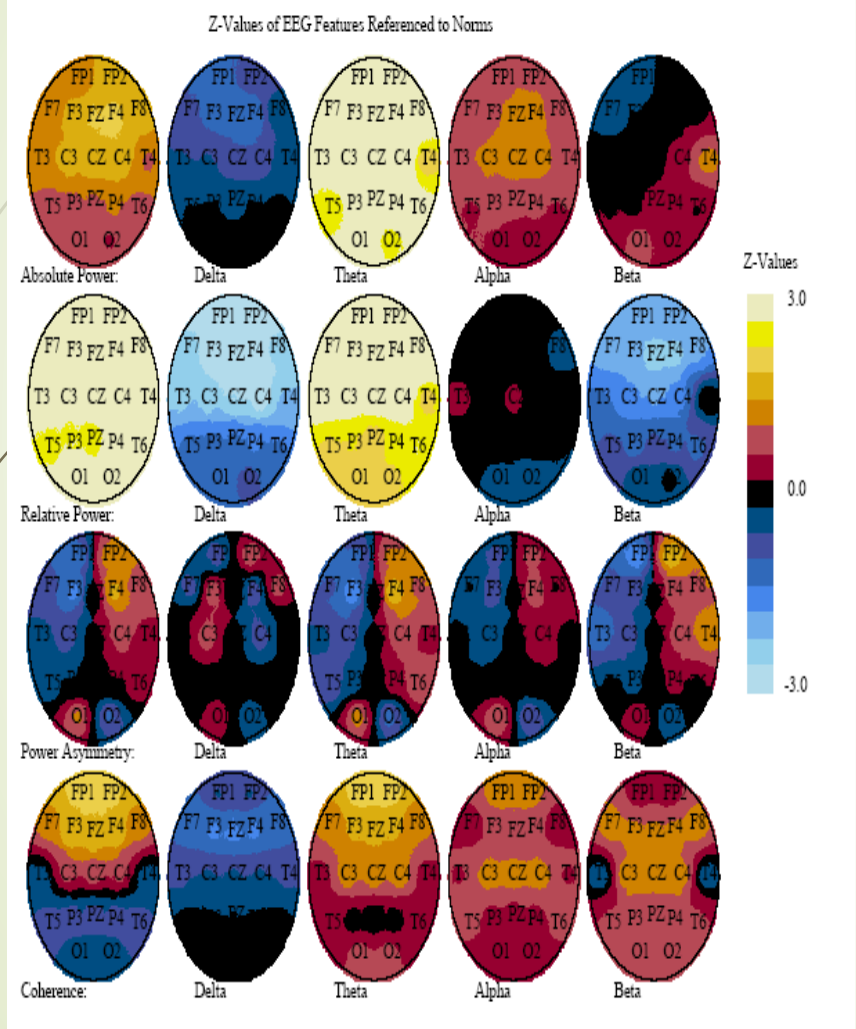
Healthy controls | **Obsessive Compulsive Disorder**





Theta

Pre



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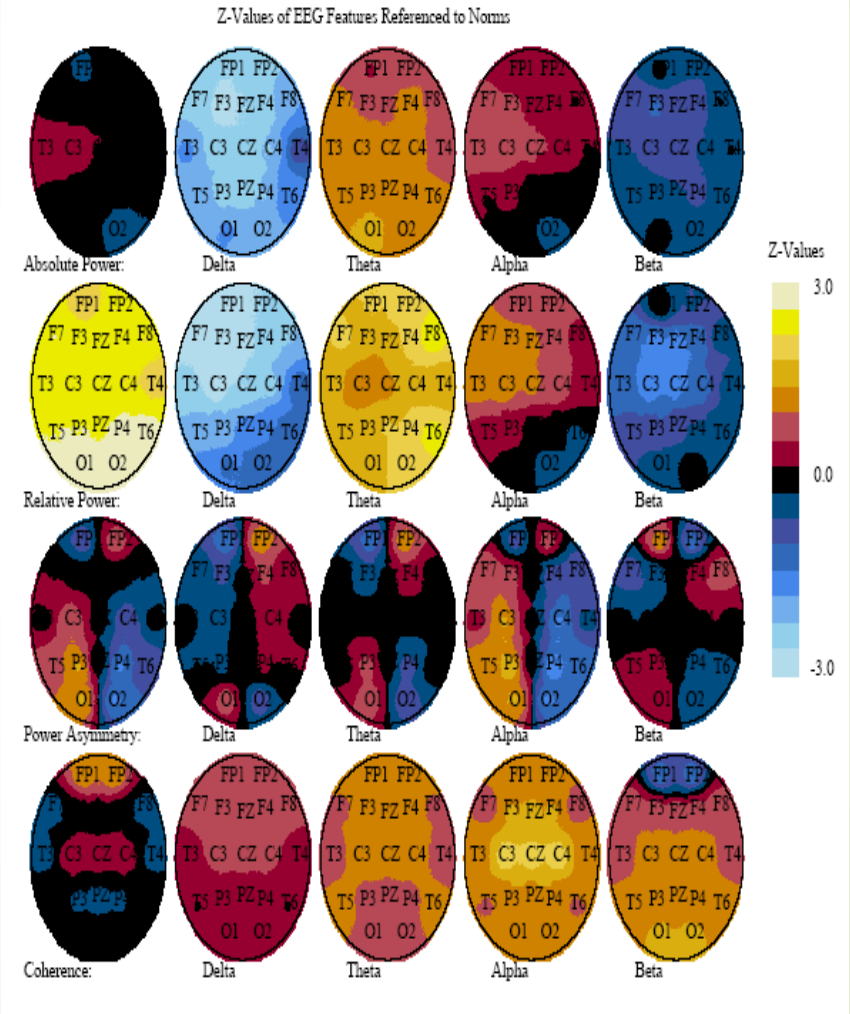


Surmeli et al., (2011)	QEEG guided NF	OCD 36 drug resistant pts	reduced the YBOC scale total score from 27.58 (±9.65 std) to 6.06 (±10.36), a reduction of 21.53 points. 2 years f/up, 33 of the pts remained symptom-free.
Sherwood, Weisend, Kane & Parker (2016); Hosseini et al. (2016)	sham controlled rtfMRI regulation NF training of the OFC (up-and-down-regulation)	Contamination anxiety.	Only in the experimental group, produced connectivity decrease, in regions associated with emotional arousal (eg, insula, hippocampus, parahippocampal and entorhinal cortices, right amygdala, brain stem, substantia nigra, temporal pole, superior temporal sulcus, thalamus, fusiform gyrus) and a correlative increased connectivity in core regions for emotional regulation (eg, right lateral PFC).

Kopřivová et al. (2013)	**RCT, double-blind, parallel design, plasebo controlled independent component NF on EEG and clinical symptoms**	**OCD (inpatients)**	**The NF group showed significantly higher percentage reduction of compulsions**
Scheinost et al. (2013)	**sham fMRI-NF controlled**	**Healthy subjects with contamination anxiety**	**enhanced control of the activity of orbitofrontal cortex (OFC) reduced contamination anxiety many days after completing the training.**
Scheinost et al. (2014)	Controlled rtfMRI NF	Healthy and **OCD** decreasing contamination anxiety symptoms in both	significant clinical improvement in OCD patients

Mild Traumatic Brain Injury (mTBI)

- A pioneering study showed the probability of the improvement of the disturbed electrical activities with NF after mTBI.
- Ayers (1987) showed the patients that received the NF for TBI reported a reduction in symptoms such as anxiety, anger outbursts, and mood issues **compared to psychotherapy**.
- Patients with TBI usually find NF treatment more tolerable and NF has been found to **improve cognitive and executive functions, memory, motor recovery, attention and seizures following TBI**. (Byers, 1995; Silver, McAllister & Yudofky, 2011)

- In a review of NF studies, May, Benson, Balon & Boutrous (2013) concluded that all studies demonstrated positive findings, in that NF led to improvement in measures of impairment, whether subjective, objective, or both.
- However, **placebo-controlled studies were lacking**, some reports omitted important details, and study designs differed to the point where effect size could not be calculated quantitatively.

- **Controlled** (Timothy, Tinius & Tinius, 2000; Keller, 2001; Rajakumari et al., 2014; Reddy, 2014; Bennett et al. 2017) and **randomized controlled** (Schoenberger, Shif, Esty, Ochs & Matheis, 2001; Rostami et al.,2017) **NF studies showed significant improvement in NF group in mTBI**.
- Munivenkatappa, Rajeswaran, Indira Devi, Bennet & Upadhyay (2014) showed significant **increase in cortical gray matter volumes, fractional anisotropy and cortical white matter tracts** in young moderately injured TBI patients after NF treatment (no control group).

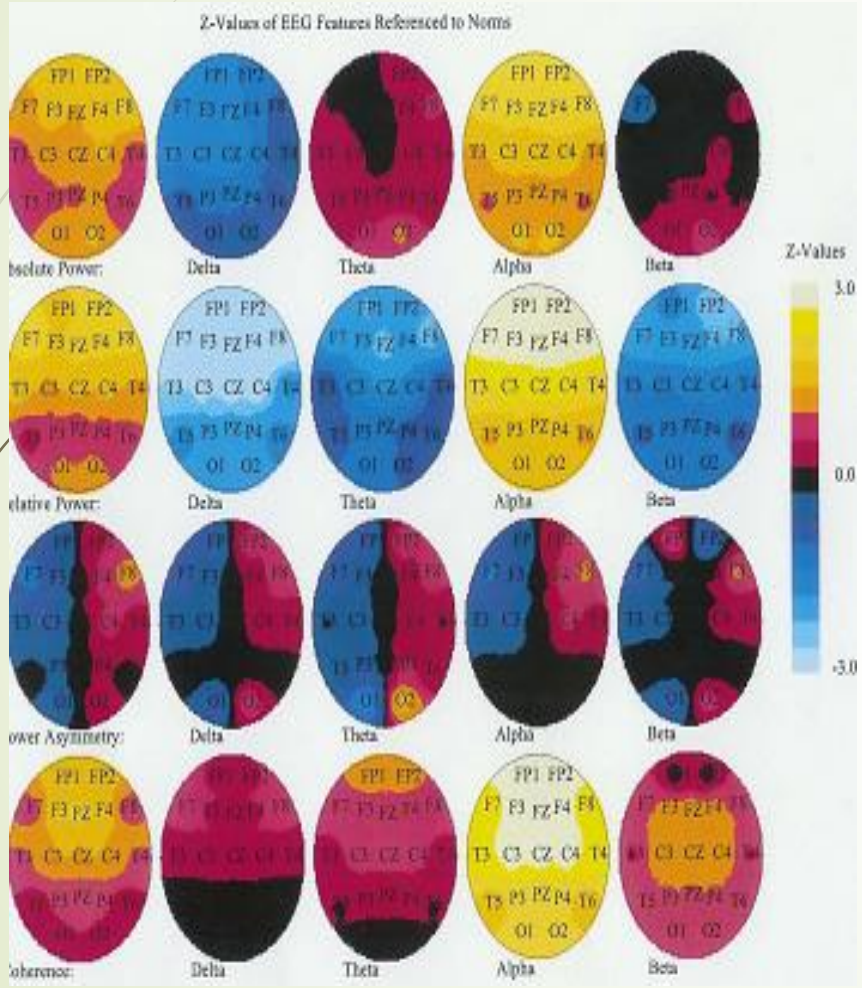
Surmeli et al. (2017)	QEEG guided NF	chronic group of mTBI patients 40 patients in PCS induced psychiatric disorders such as MDD, bipolar, OCD, GAD, panic disorder, insomnia, ADHD, psychosis, alcohol and drug abuse	the Hamilton Depression (HAM-D) showed a decrease in depression symptoms where the score of the group decreased to 0 from 15.58. Cured them no one's symptoms relapsed in follow-up length of 3.1 years

- The double blind sertraline study of Ashman et al. (2009) in TBI induced MDD showed response (defined as a decrease of the HAM-D score by 50% or a drop below 10) in 59% of the subjects
- Using the same criteria, the response in Surmeli et al. (2017) study was

  95%, and 93% of the group decreased their scores to 0.
- The group mean was reduced from 15.58 (moderate depression) to 0.55.
- This is an overall reduction of 15 points, and at $P < .001$ level of significance
- Given the effect size of the NF treatment with 93% to 95% decrease in the **HAM-D r**ating scale to 0,
- **It is difficult to explain such strong effect size based on a placebo factor and thi**s **result compares with the double blind study given by Ashman et al (2009).**

Alpha and alpha hypercoherence

Pre



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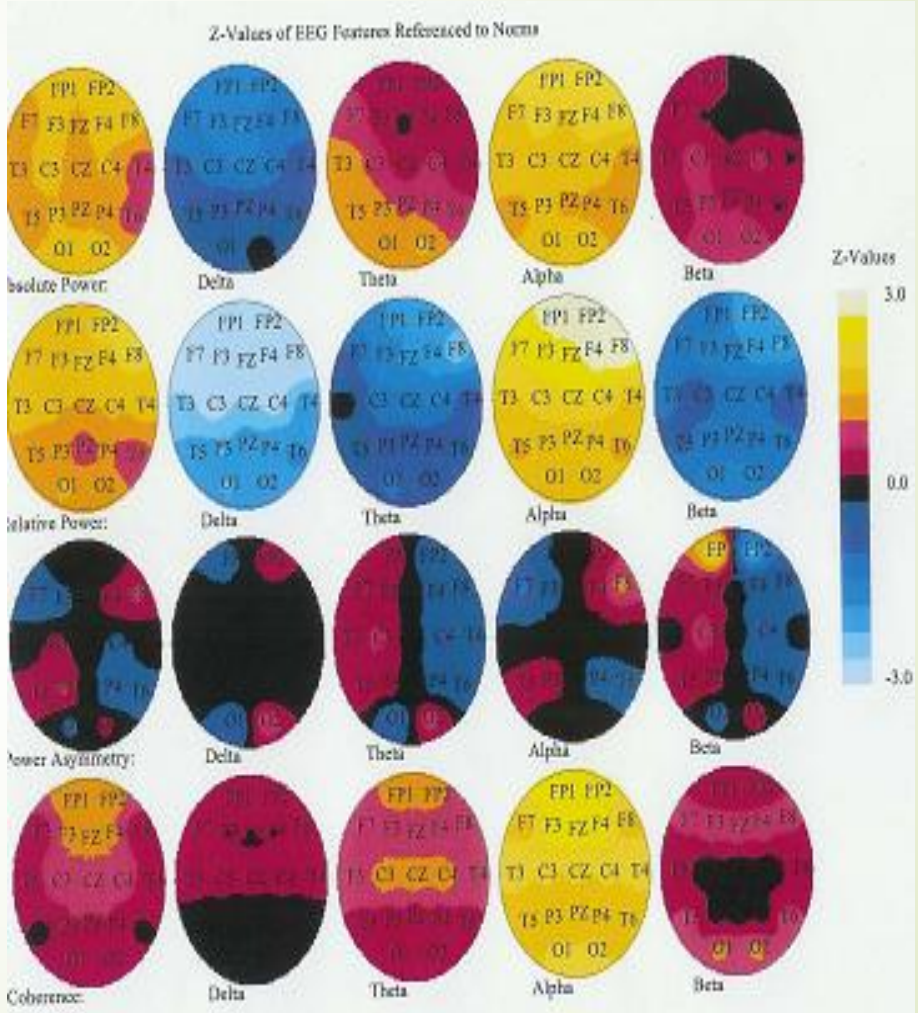
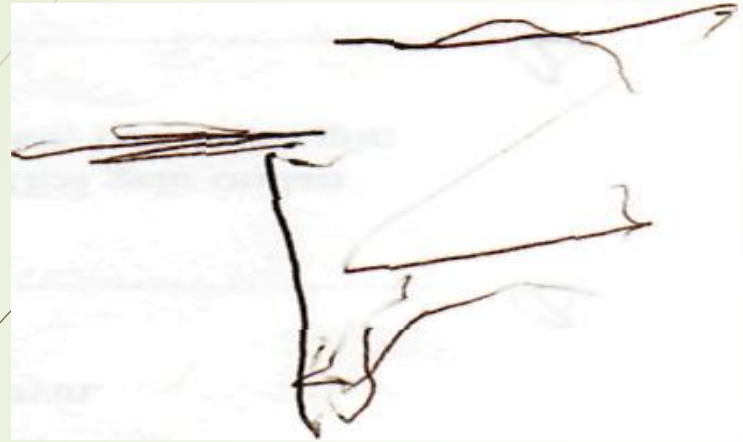
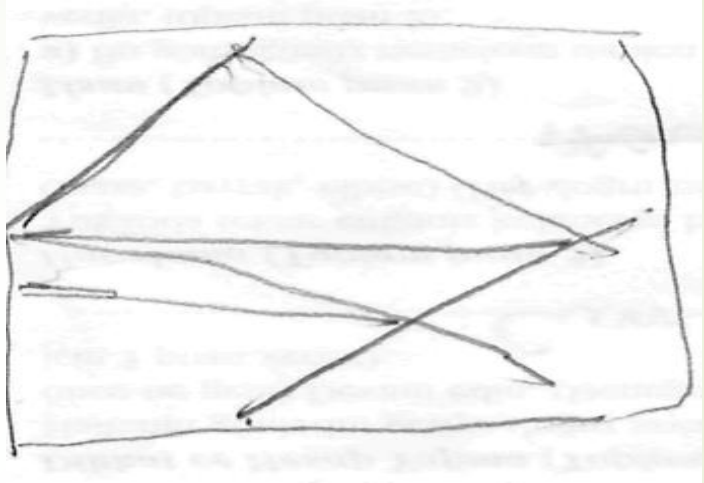


Constructional Ability in Alzheimer's Disease

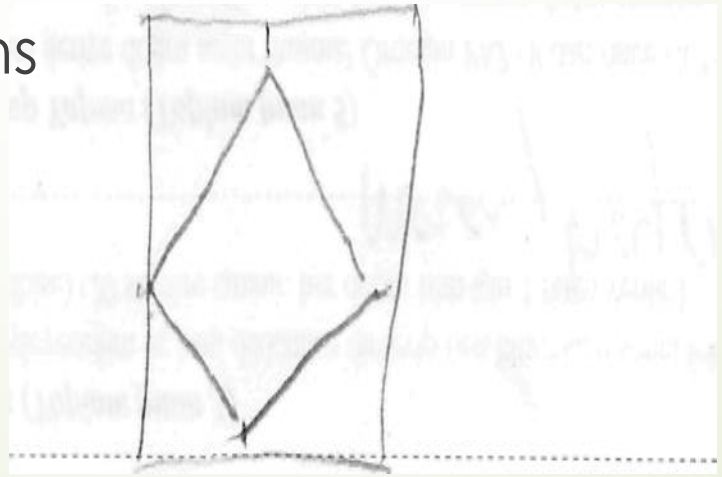
Baseline



30 Sessions NF (each session lasts1 h)

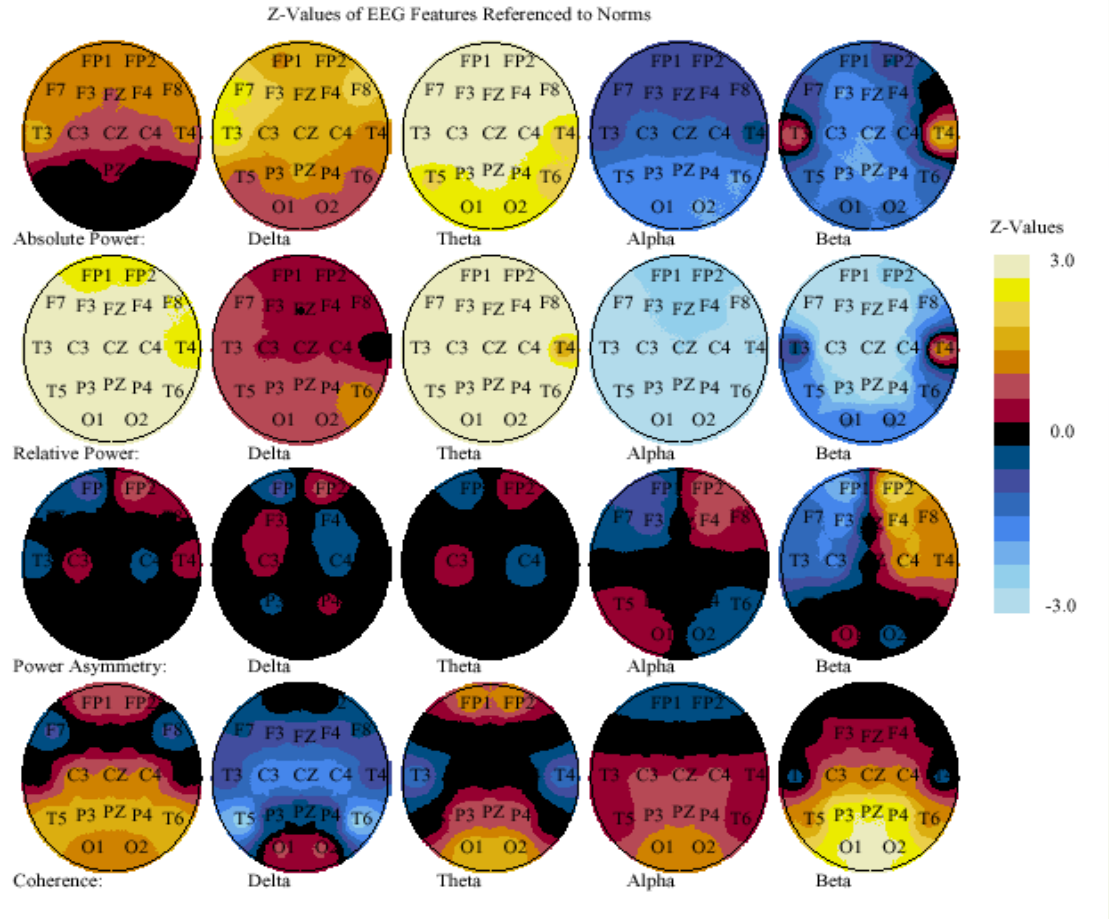


- 35 Sessions

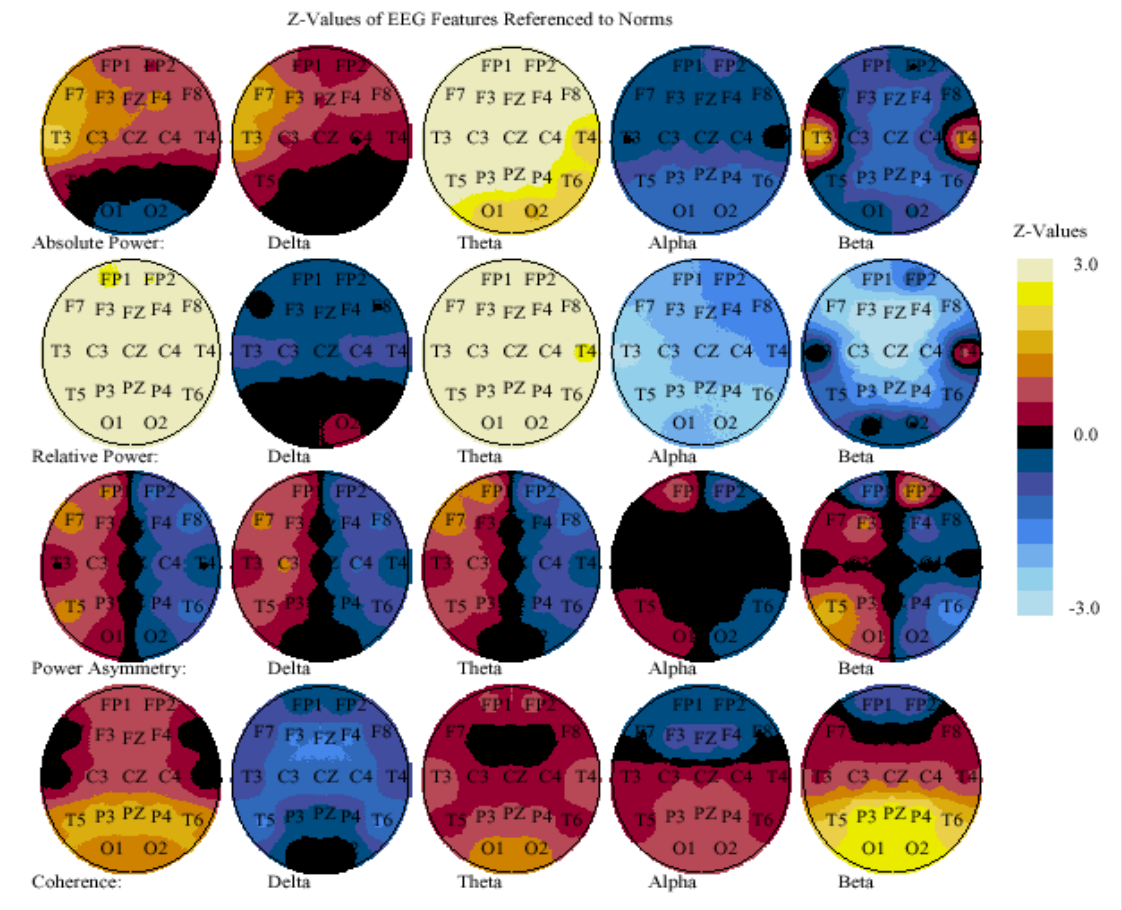


Alzheimer's Disease

Baseline

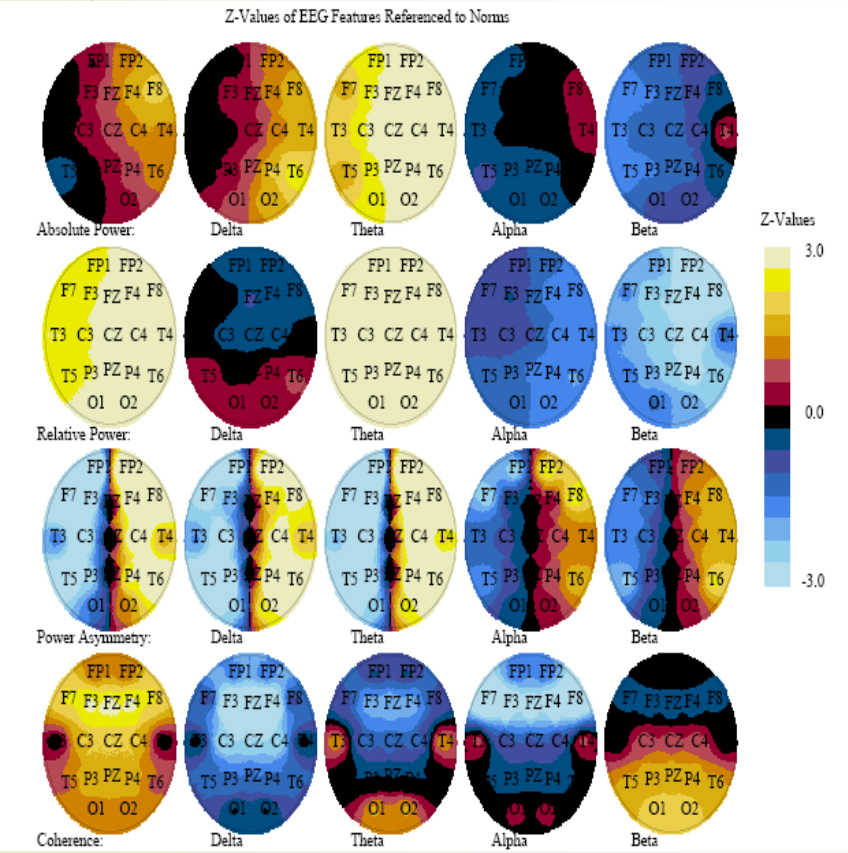


Post treatment

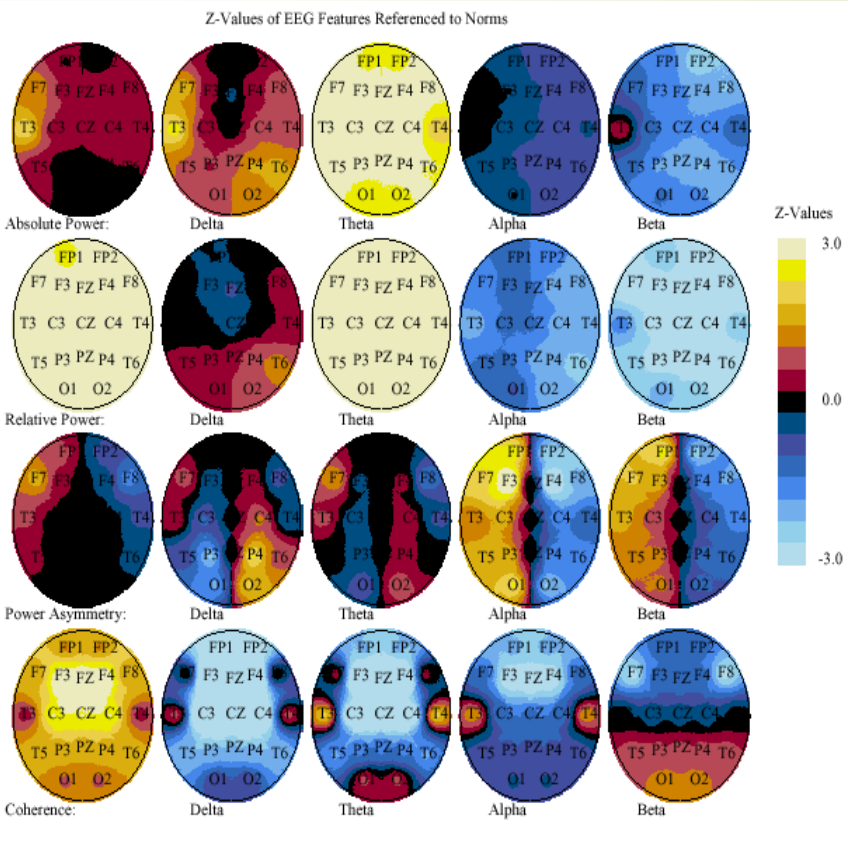


VASCULER DEMENTIA

Baseline



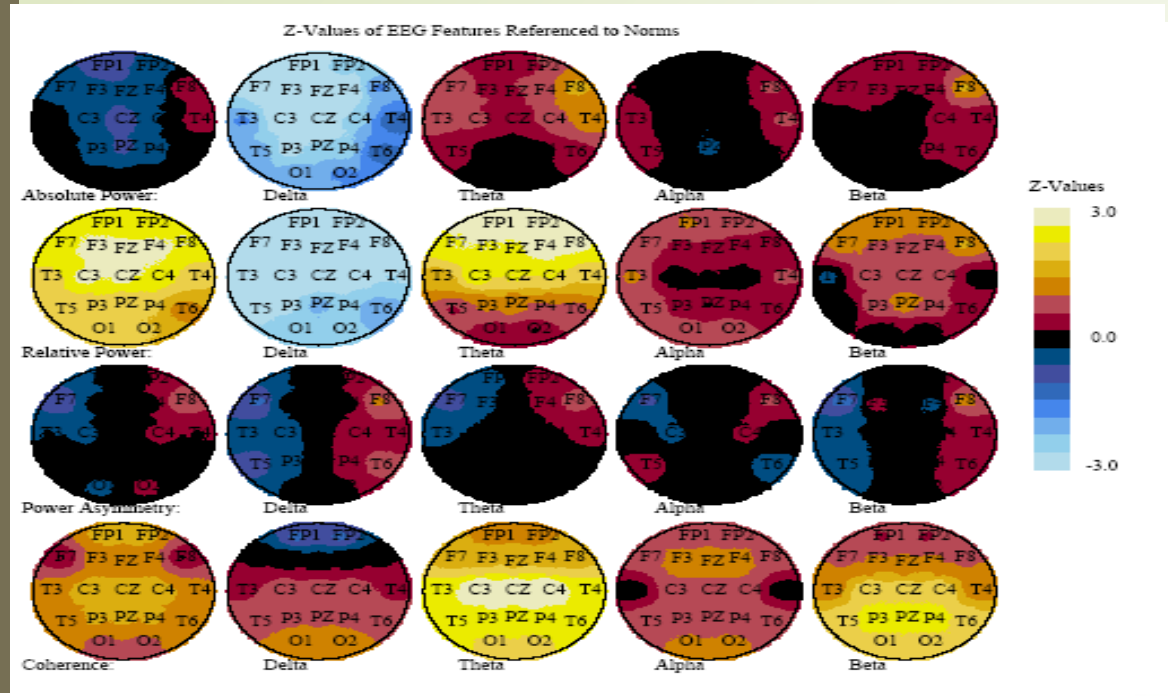
Post treatment

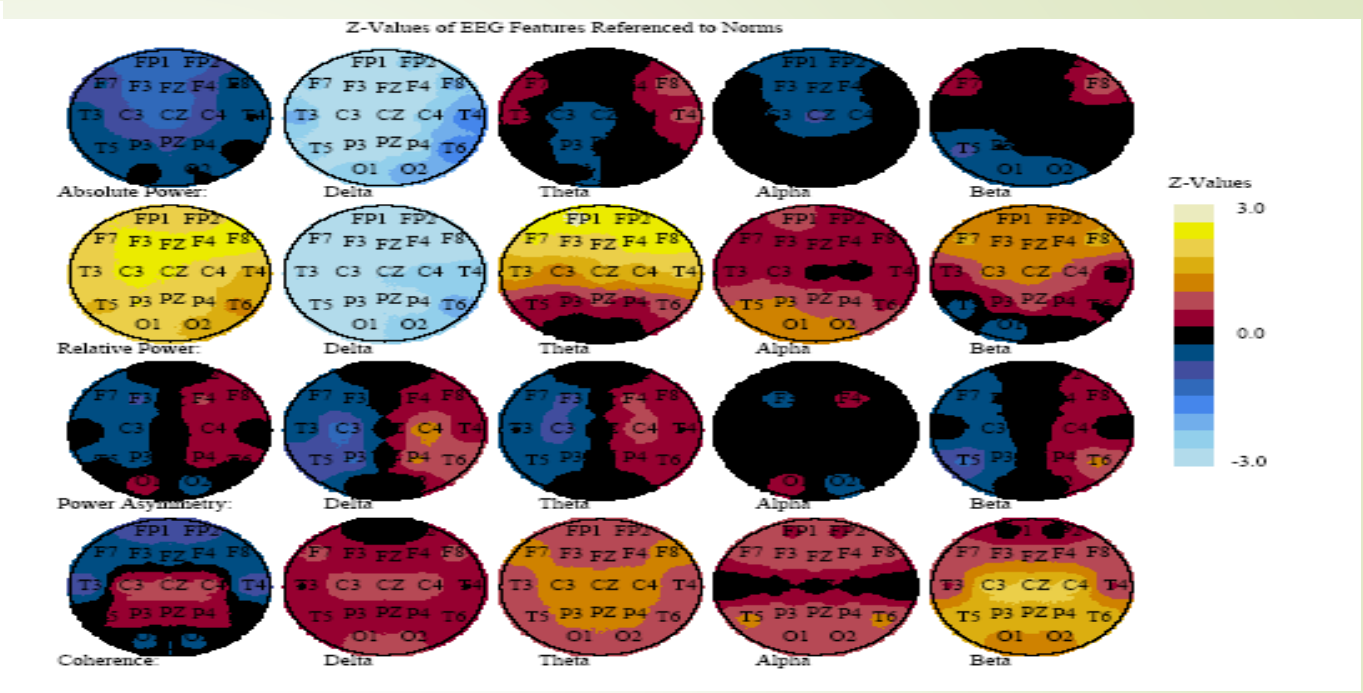


Angelakis et al., 2007; Becerra et al., 2012; Gomez-Pilar, Corralejo, Nicolas-Alonso, Álvarez & Hornero, 2016; Lecomte & Juhel, 2011; Staufenbiel, Brouwer, Keizer & van Wouwe (2014); Rana et al., 2016	**Neurofeedback**	**to improve cognitive performance in the healthy elderly**	**mixed success.**
Festa, Heindel, Connors, Hirschberg & Ott (2009)	controlled study	Early-stage Alzheimer's disease	improved in selective improvement in the efficiency of processing within the **posterior sensory cortical network** in NF group
Berman & Frederick (2009)	waiting list control compared NF study	Dementia	improved memory and some aspects of executive function in NF group.

Jirayucharoensak, Israsena, Pan-ngum & Hemrungrojn (2014)	Decrease the ratio of Theta/Alpha controlled NF study,	MCI and healthy groups.	improved level of cognitive ability in both
Luijmes, Pouwels & Boonman (2016)	NF	ALZHEIMER	improved learning memory and increased recognition/recall of information.
Surmeli et al. (2015)	qEEG-guided NF training in dementia **(Alzheimer's type, and Vascular dementia)** **No medications**	This was the first time the same modality was shown to be beneficial in **both dementia groups.**	average increase of **6 scores** for all subjects regardless of dementia type (both group) with **Mini Mental Status Examination scores**

- Birks & Harvey (2006) reviewed **16 randomized controlled** trials showing that **donepezil** improved the cognitive functions in both 5 and 10 mg/d **after 6 months**, about **1.5 points** on the **MMSE versus placebo groups**, and in 10 mg/d after 52 weeks (about **2 points** on MMSE).
- **According to the results of Surmeli et al. (2015), an average 6-point increase in the MMSE scores were observed during a treatment period from 1 to 6 months.**





Monopolar Interhemispheric Coherence (Z)

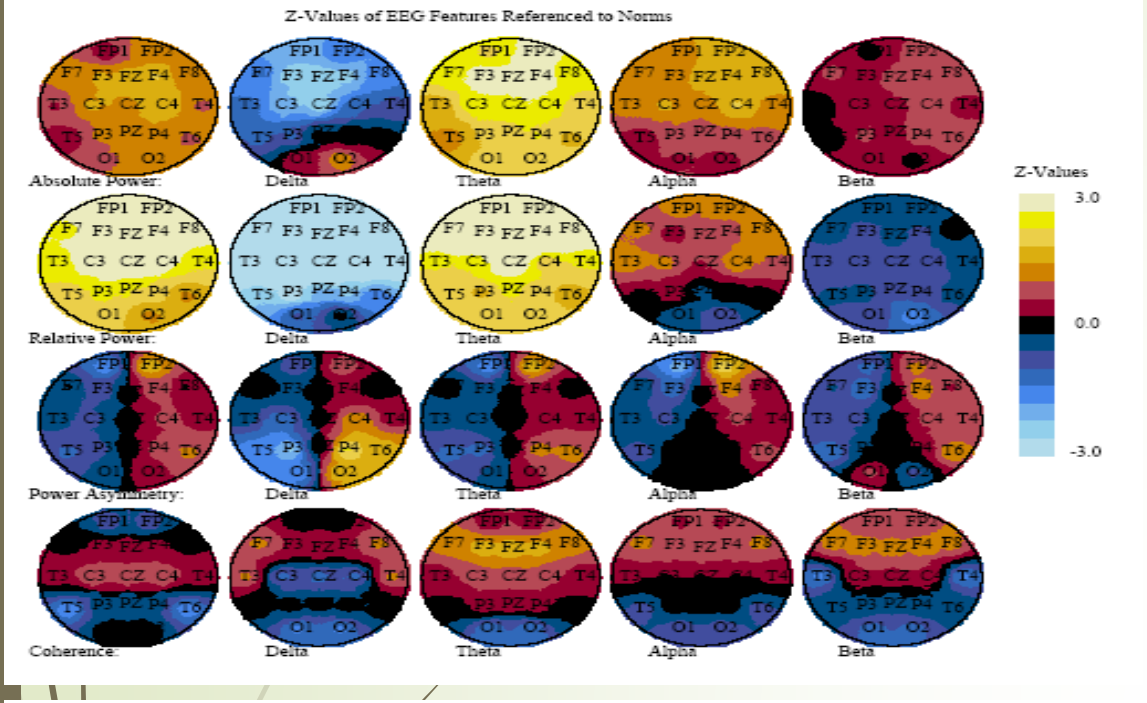
	Fp1-Fp2	F3-F4	C3-C4	P3-P4	O1-O2	F7-F8	T3-T4	T5-T6
Total	0.49	1.29	1.88	1.45	1.66	1.15	1.63	1.46
Delta	-1.11	0.14	0.93	1.08	1.39	0.10	0.55	0.98
Theta	1.38	1.81	3.27	2.55	2.20	1.56	2.41	2.41
Alpha	0.98	1.26	0.98	0.99	1.19	0.91	-0.14	1.05
Beta	0.63	1.17	2.28	2.44	2.22	0.90	1.18	2.24
Comb.	1.60	1.20	1.79	1.50	0.97	0.28	1.10	1.26

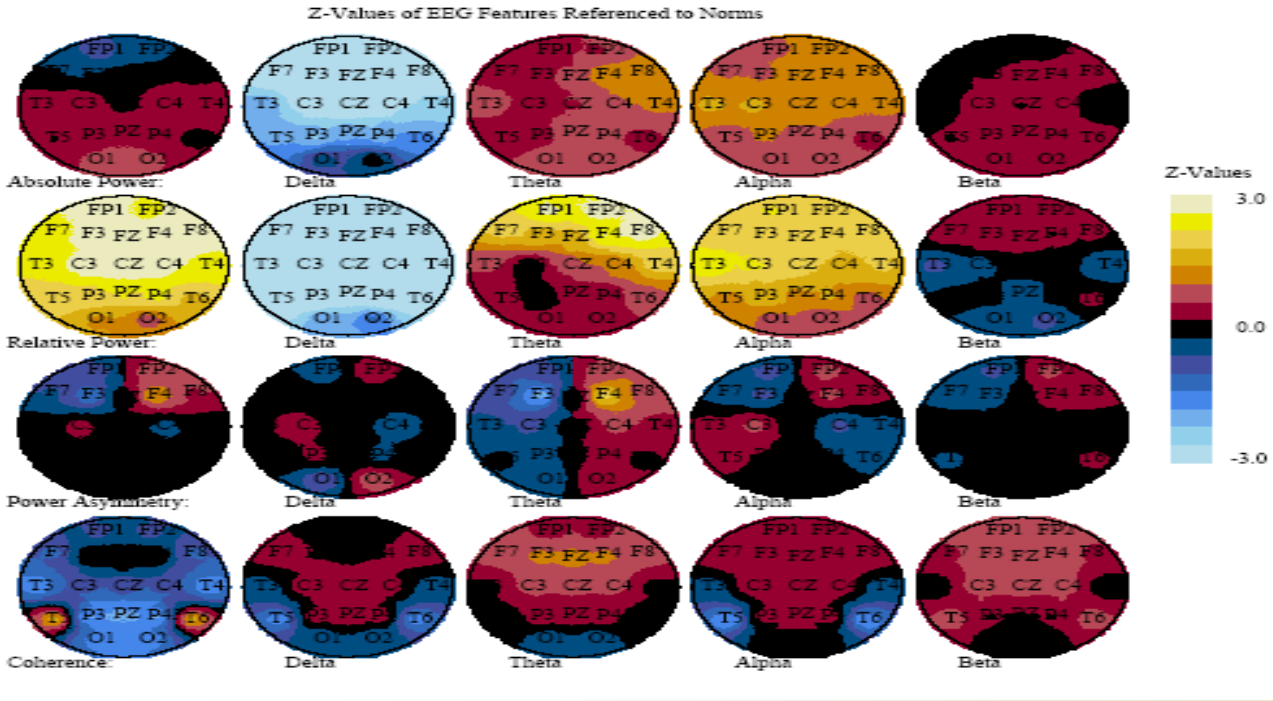
	Lateral	Medial	Anterior	Central	Posterior	Head
Total	1.20	1.32	0.60	1.35	1.25	1.39
Delta	-0.32	0.50	-0.30	0.19	0.79	0.13
Theta	2.00	2.36	1.33	2.03	1.89	2.61
Alpha	0.02	0.62	0.64	-0.01	0.61	0.34
Beta	1.37	1.96	0.38	1.38	2.02	2.08
Comb.	1.18	2.45	1.50	1.88	1.64	2.36

Monopolar Interhemispheric Coherence (Z)

	Fp1-Fp2	F3-F4	C3-C4	P3-P4	O1-O2	F7-F8	T3-T4	T5-T6
Total	0.33	0.83	0.68	0.92	1.28	1.03	0.72	1.13
Delta	0.15	0.33	0.95	0.47	0.78	0.78	0.21	0.38
Theta	0.79	0.97	1.49	1.13	1.09	1.21	0.73	0.98
Alpha	0.60	0.92	0.16	0.83	1.04	0.89	-0.29	1.15
Beta	0.14	1.01	2.00	1.81	1.33	0.75	0.65	1.69
Comb.	-0.92	-0.34	0.83	0.55	-0.36	-0.51	-1.04	0.28

	Lateral	Medial	Anterior	Central	Posterior	Head
Total	0.39	0.11	0.11	0.00	0.71	0.12
Delta	-0.76	-0.66	-0.80	0.04	-0.41	-1.02
Theta	0.44	0.70	0.51	0.78	0.59	0.56
Alpha	0.14	-0.13	0.26	-1.58	0.52	-0.20
Beta	0.67	1.28	-0.02	1.08	1.37	1.19
Comb.	-0.88	-0.30	-1.08	0.17	-0.06	-0.68





Monopolar Power Z-scores

	Fp1	Fp2	F3	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
Total	0.48	1.20	1.54	1.95	1.56	1.83	1.11	1.44	1.05	1.25	1.14	1.19	0.61	1.09	0.38	1.07	1.61	1.46	1.23
Delta	-2.25	-1.52	-2.53	-2.43	-2.15	-1.26	-1.18	0.03	0.55	1.32	-1.48	-1.71	-1.39	-0.98	-1.13	0.19	-2.64	-2.52	-0.12
Theta	2.25	2.85	3.09	3.42	2.54	2.63	1.93	2.34	2.02	2.18	2.50	2.35	1.52	2.01	1.23	1.80	2.96	2.68	2.21
Alpha	1.34	1.85	1.29	1.83	1.59	1.94	1.03	1.09	0.62	0.55	1.48	1.68	1.13	1.35	0.38	0.86	1.60	1.29	0.72
Beta	0.16	0.72	0.39	0.84	0.64	0.86	0.76	0.86	0.57	0.14	0.71	1.08	-0.18	0.56	-0.04	0.84	0.88	0.58	0.58
Comb.	3.17	3.01	3.66	3.68	3.50	3.06	2.38	1.95	1.58	1.23	2.73	3.05	2.77	2.46	2.05	1.28	3.76	3.79	1.95

	LLat	RLat	LMed	RMed	LAnt	RAnt	LCen	RCen	LPos	RPos	LH	RH	Mid	Ant	Cent	Post	Head
Total	0.08	0.69	0.82	1.29	0.74	1.20	0.75	1.10	0.38	0.84	0.60	1.16	1.05	1.09	1.04	0.69	0.95
Delta	1.02	0.76	1.77	1.32	1.90	1.63	1.43	0.77	0.54	0.16	1.62	1.19	1.66	2.09	1.61	0.19	1.77
Theta	1.48	1.66	2.01	2.27	2.12	2.21	1.56	1.70	1.37	1.61	2.01	2.26	1.97	2.42	1.95	1.62	3.04
Alpha	0.66	0.95	0.84	1.29	0.98	1.37	0.97	1.28	0.04	0.31	0.79	1.25	0.88	1.25	1.19	0.09	1.01
Beta	-1.10	0.21	-0.73	-0.12	-0.70	0.40	-0.75	0.00	-0.38	-0.03	-1.15	-0.09	-0.04	-0.03	-0.55	-0.33	-0.62
Comb.	4.53	4.41	6.29	5.69	5.75	6.07	3.91	3.32	3.25	2.04	6.10	5.54	6.24	6.41	6.16	2.87	6.28

Monopolar Power Z-scores

	Fp1	Fp2	F3	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	Fz	Cz	Pz
Total	-0.88	-0.51	-0.27	0.28	0.69	0.50	0.57	0.51	0.70	0.78	-0.26	0.17	0.44	0.32	0.28	0.12	-0.03	0.17	0.66
Delta	-3.74	-3.11	-3.98	-4.11	-2.92	-2.84	-2.31	-2.23	-0.57	-0.09	-3.11	-3.48	-2.09	-2.50	-1.93	-1.73	-4.07	-3.60	-1.91
Theta	0.41	0.68	0.53	1.38	0.68	1.01	0.50	0.75	0.88	1.02	0.66	1.24	0.76	1.19	0.49	0.52	0.74	0.60	0.89
Alpha	1.03	1.16	1.04	1.32	1.55	1.27	1.14	1.04	0.89	0.87	1.05	1.29	1.51	1.19	0.75	0.50	1.31	1.28	1.06
Beta	-0.18	0.17	0.25	0.42	0.43	0.35	0.58	0.50	0.44	0.30	0.15	0.42	-0.18	-0.29	0.25	0.45	0.51	0.22	0.37
Comb.	3.07	2.74	3.30	3.60	3.08	3.11	2.42	2.71	1.37	0.74	2.72	3.43	2.92	2.99	2.37	2.13	3.57	3.46	2.54

	LLat	RLat	LMed	RMed	LAnt	RAnt	LCen	RCen	LPos	RPos	LH	RH	Mid	Ant	Cent	Post	Head
Total	-1.39	-1.97	-0.30	-0.63	-0.46	-1.15	-0.23	-0.56	-0.39	-0.41	-0.75	-1.16	-0.74	-1.05	-0.84	-0.51	-1.04
Delta	1.99	2.24	2.69	2.53	2.87	2.66	1.91	2.05	1.40	1.29	2.69	2.67	2.36	3.24	2.51	1.49	4.03
Theta	-0.19	0.59	-0.35	0.48	-0.50	0.73	0.09	0.70	-0.08	0.20	-0.43	0.50	0.10	0.24	0.27	0.07	-0.09
Alpha	0.72	0.60	0.74	0.76	0.61	0.90	1.12	0.85	0.43	0.26	0.75	0.71	0.84	0.80	1.05	0.36	0.64
Beta	-2.49	-1.15	-1.33	-1.52	-2.15	-1.02	-1.35	-1.35	-0.70	-0.80	-2.06	-1.73	-0.97	-1.53	-1.94	-0.99	-1.59
Comb.	4.86	5.81	5.56	5.64	5.26	6.13	3.67	3.68	3.46	3.13	5.72	6.08	5.95	6.16	6.05	3.64	6.31

Schneider & Pope (1982)	NF	SCHIZOPHRENIA	the EEG of schizophrenics temporarily altered using NF in a way that mimics the EEG changes that have been shown to occur with neuroleptic-induced clinical improvement
Schneider et al., 1992; Hardman et al., 1997; Gruzelier, Hardman, Wild & Zaman, 1993	In controlled studies on SCPs	SCHIZOPHRENIA	improvement in cognitive functions
Ruiz et al. (2013)	r-fMRI NF	SCHIZOPHRENIA	able to train the self-activation of the right insula improved performance on a face recognition task
Cordes et al., 2015	fMRI NF control of the anterior cingulate cortex	SCHIZOPHRENIA	Schizophrenia patients activated the dorsal of the anterior cingulate cortex; healthy controls the rostral subdivision of the AC cortex

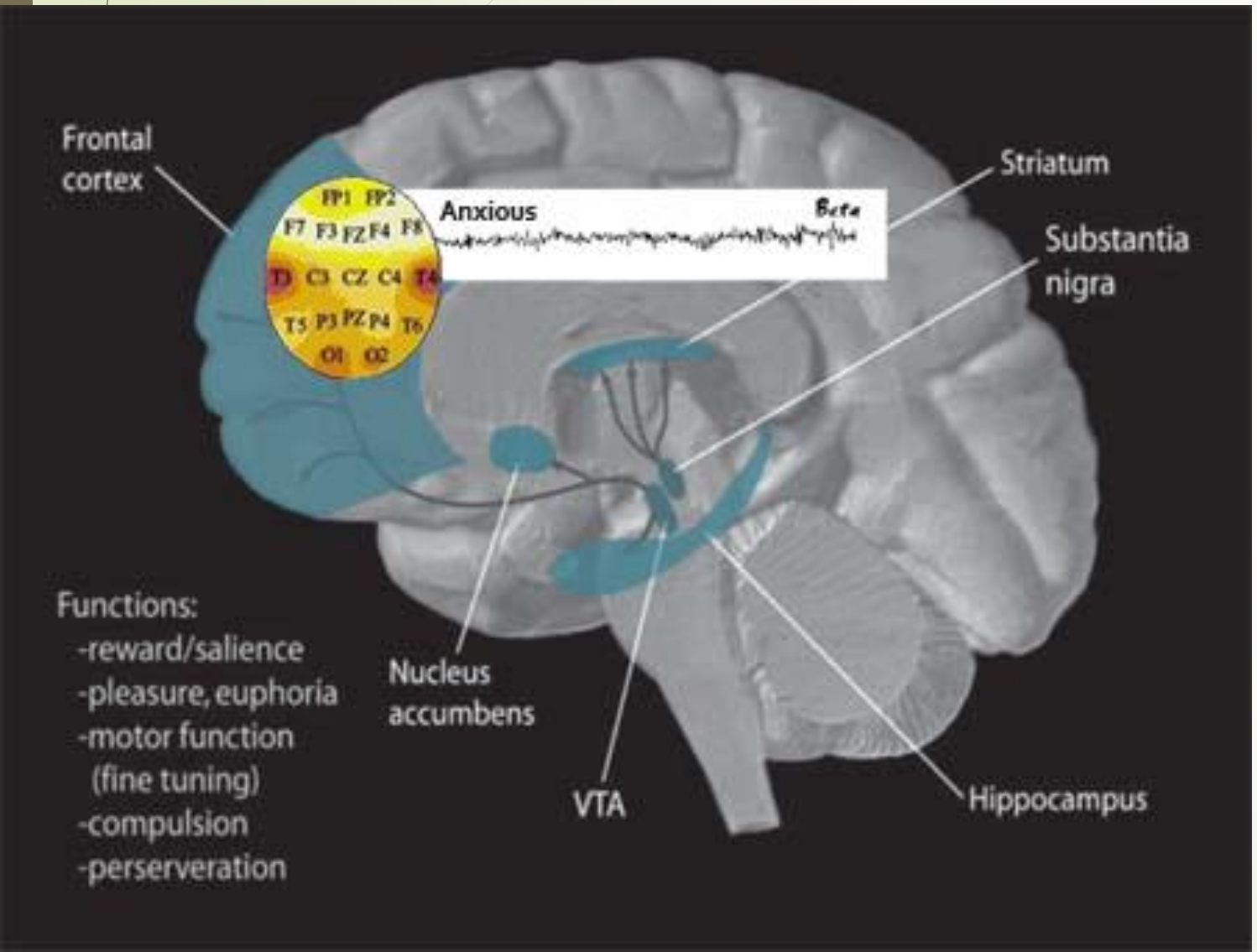
Surmeli et al. (2012)	**QEEG guided neurofeedback**	**SCHIZOPHRENIA** **(N: 51)**	**47 out of 48 patients** showed clinical improvement as indicated by changes in their **PANSS scores,** where the group's mean score of **110.24 (SD 21.62) decreased to 19.56 (SD 26.78).** **The average reduction in PANSS scores was 83%,** which was above the **20% change seen when only antipsychotic medications were used.**

- There is an accumulation of evidence that particular microstate networks are selectively affected in schizophrenia.
- a systematic **meta-analysis** over all studies available to date relating **EEG microstates to schizophrenia** results showed medium size effects for two classes of microstates, namely, **a class C that was found to be more frequent in schizophrenia** and **a class D that was found to be shortened compared to healthy controls** and this shortening was correlated with the **presence of core symptoms of schizophrenia**, e.g., **positive psychotic symptoms, insufficient reality testing and self-monitoring as during auditory verbal hallucinations**.
- As interventional studies have shown that these microstate features may be systematically affected using **antipsychotic drugs or NF interventions**, these findings may help introduce novel diagnostic and treatment options. (Rieger, Diaz Hernandez, Baenninger & Koenig, 2016)

Diaz Hernandez, Rieger, Baenninger, Brandeis & Koenig (2016)	**Microstate D NF**	**Microstate-NF training proved feasible in healthy subjects.**	**The implementation of the same protocol in schizophrenia patients may promote skills useful to reduce positive symptoms by microstate NF.**
Nan et al. (2017)	intensive NF training	SCHIZOPHRENIA.	EEG changes by NF training, observable cognitive and behavioral improvements, such as short-term memory, mood, and speech patterns after training.
Dyck et al. (2016)	fMRI-NF	SCHIZOPHRENIA. (patients with ongoing AVHs)	subjective improvement concerning disturbance through and suffering from voices, as well as decrease in their number, intensity, and negativity.

Mohammadi, Bahrami, Hatef & Kargar (2018)	**randomized controlled NF study**	**SCHIZOPHRENIA AND BIPOLAR DISORDER**	**expressive empathy and emotional empathy subscales increased in both**
Rieger, Rarra, Diaz Hernandez, Hubl & Koenig (2018)	NF training to modulate the uditory-evoked N100 component in patients and associated auditory verbal hallucinationsor another unrelated component or P200 (control).	SCHIZOPHRENIA	Control group showed symptom improvement in the PANSS total scores; a correlation between learning and improvement found in AVHs across training sessions.
Orlov et al. (2018)	**rtfMRI-NF training on functional connectivity between the superior temporal gyrus (STG) and other speech and language regions**	**SCHIZOPHRENIA treatment-refractory Auditory verbal hallucinations (AVH)**	**increased functional connectivity between the left STG, the left inferior prefrontal gyrus (IFG) and the inferior parietal gyrus. associated with a reduction in AVH symptoms over the training period.**

Dopamine pathways



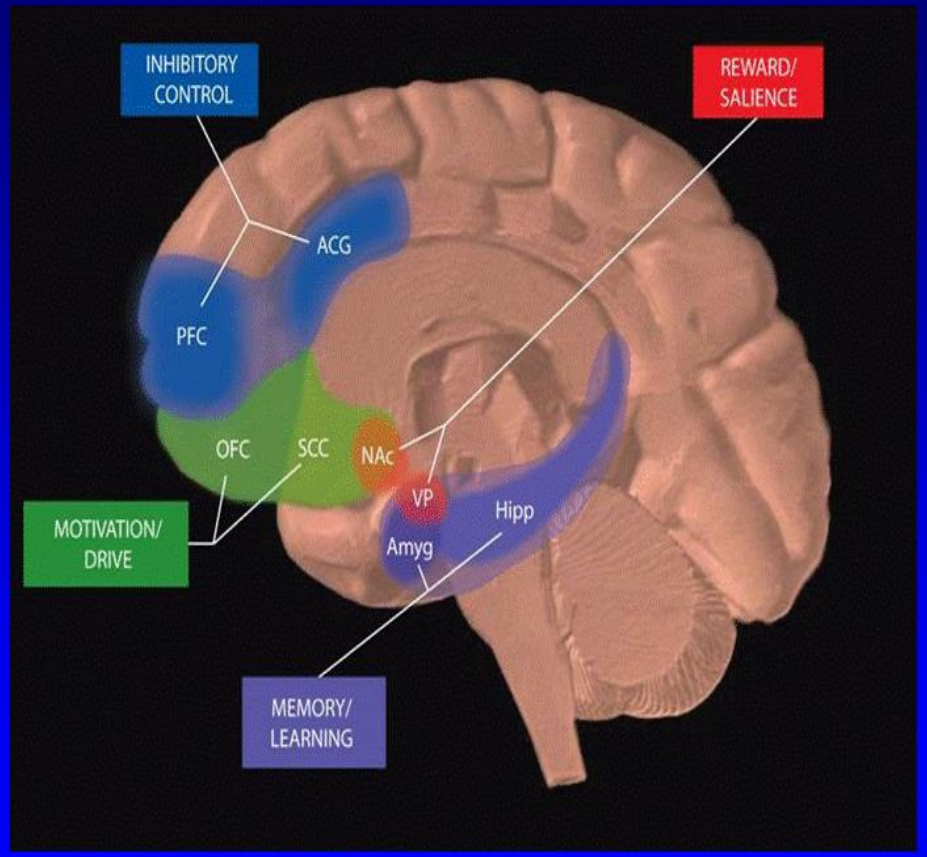
- Stanford study **31 healthy** subjects:
- The **Nucleus accumbens** (NAcc) plays critical roles in healthy **motivation and learning**, as well as in psychiatric disorders (including **schizophrenia and ADHD**).
- Individuals who recruited positive aroused affect were better able to **increase NAcc activity in response to Neurofeedback**, and that NAcc Neurofeedback also elicited functionally correlated activity in the **medial prefrontal cortex** (Greer SM. et al, 2014).

Healthy subjects Substantia nigra/ventral tegmental area complex (SN/VTA): cingulate cortex

- Neurofeedback-mediated self-regulation of the **dopaminergic midbrain**.
- Veridical feedback improved the ability to **up-regulate**
- Substantia nigra/ventral tegmental area complex (SN/VTA) compared to baseline while inverted feedback did not (Sulzer J. et al, 2013).

- LORETA neurofeedback in the **anterior cingulate cortex** appears to induce long-term cortical changes and produces significant positive increases in working memory and processing speed scores in healthy subjects (Cannon, 2011).

Circuits Involved In Drug Abuse and Addiction

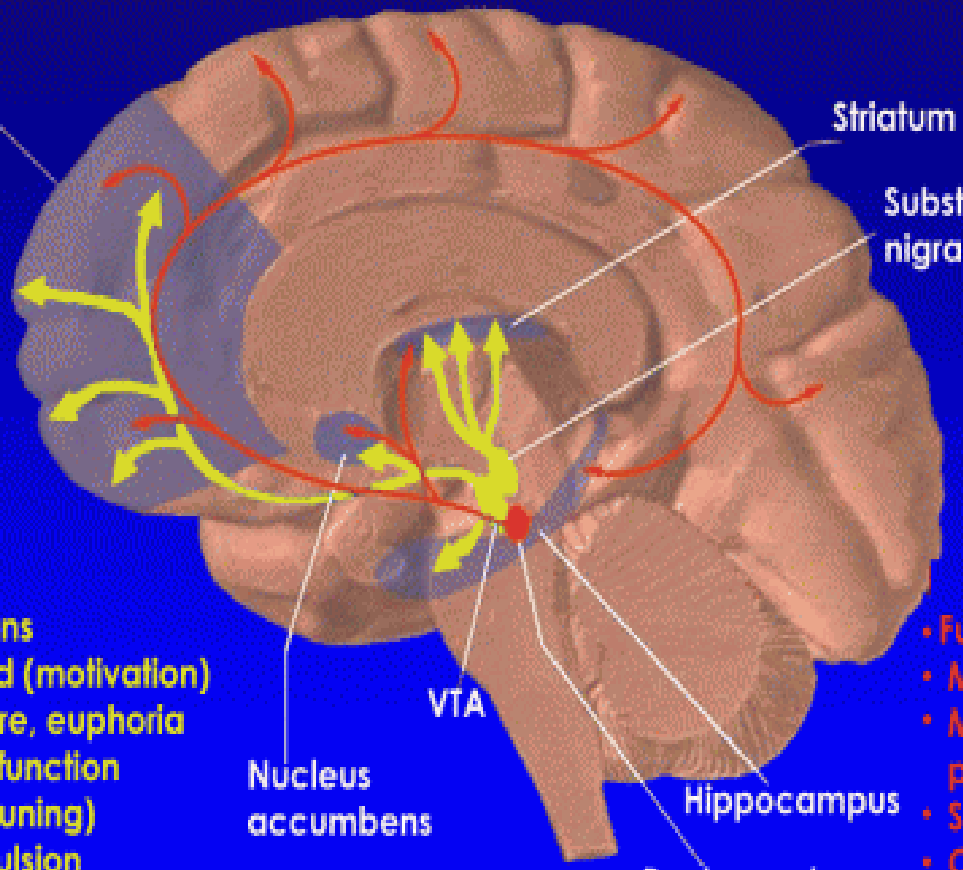


All of these brain regions must be considered in developing strategies to effectively treat addiction

NIDA

Dopamine Pathways

Serotonin Pathways

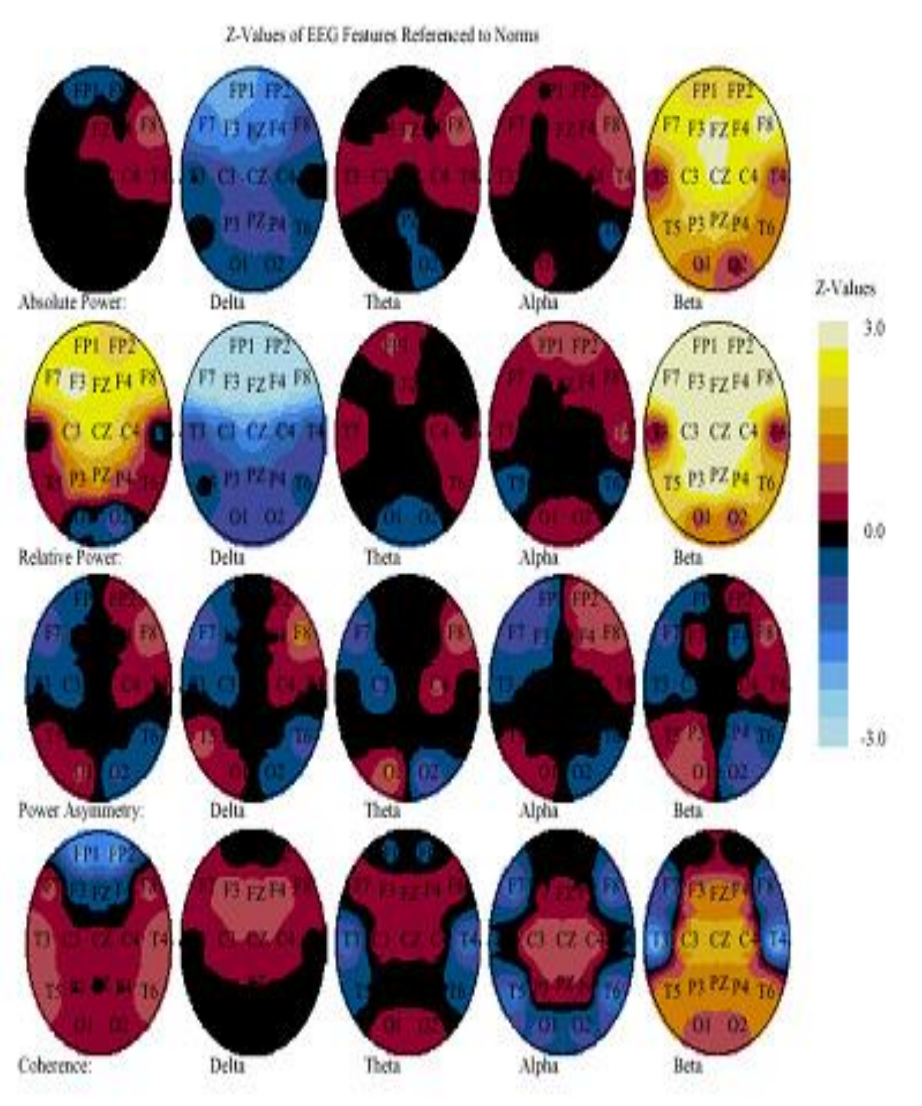


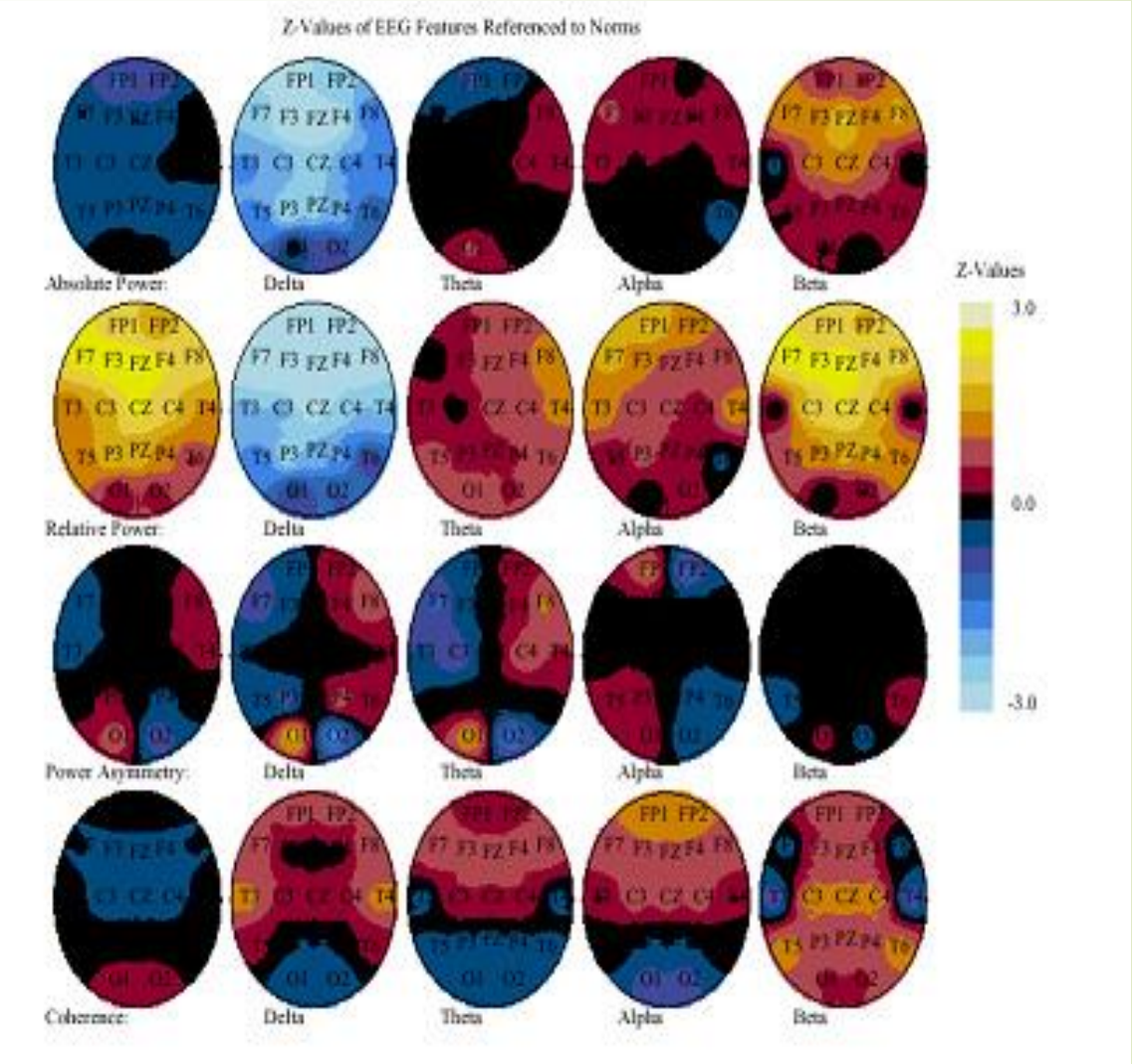
Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine-tuning)
- Compulsion
- Perseveration

- Functions
- Mood
- Memory processing
- Sleep
- Cognition

NIDA

Decreasing Beta after NF





- One of the most prominent symptoms in addiction disorders is the strong desire to consume a particular substance **(craving).**
- **Craving ranks among the most important aspects of relapse.**
- The exposure to stimuli, which have regularly been associated with drug consumption as well as addiction behaviour, can **become conditioned cues eliciting conditioned responses**, such as drug consumption and craving. (Karch et al., 2015)
- Among the medical treatment methods used in the treatment of substances, medical drugs, psychotherapies, and detox programs are the most frequently used methods. (Luigjes, Breteler, Vanneste, de Ridder, 2013)

- After more than 70 percent of Alcohol and Drug users have completed medical treatment, they are beginning to use alcohol and drugs again a few months later. (Marlatt & George,1984: Higgins et al.,1995)
- The success rate of treatment with classical methods (drugs, psychotherapy and AMATEM) is 20-44%. (Hammond, 2011)
- 60 percent of heroin addicts go back to heroin after drug treatment. (Gossop, Stewart, Browne & Marsden, 2002)
- 80 percent of cocaine addicts go back to cocaine after treatment. (Kang et al., 1991)
- 87 percent of them use Cannabis instead of using psychiatric medication used in treatment. (Lucas et al, 2015)
- Considering that many patients leave treatment early, additional methods need to be applied to keep the patient in treatment and reduce relapse. Use of methods that can be controlled by his own brain, i.e. personalized treatment is required.

- While NF has been employed since the 1970s in the treatment of alcoholism and other addictions, it remains less than a mainstream treatment. NF is not still validated as a stand-alone therapy for addictive disorders.
- NF has been added to medical treatments. (Scott, Kaiser, Othmer & Sideroff, 2005)
- Observed evidence confirms the potential for treatment success rates to be **doubled or even tripled** when added to NF therapy to traditional alcoholism, and substance abuse treatment. (Sokhadze, Cannon & Trudeau, 2008)

- There are **controlled studies showing the success of NF** in the treatment of drugs and alcohol and the success rate with NF treatment is **78%.** (Hammond DC., 2011)
- Many persons with substance use disorders have comorbid conditions (mTBI, ADHD, affective disorders and anxiety disorders) that need to be considered in designing a treatment plan that incorporates NF. (Marlatt & George, 1984)
- Increased Alpha waves can be taught with NF therapy.
- The use of alpha and theta waves in alcohol use has proven to be an effective method, first popularized by the work of Eugene Peniston, and became popularly known as the Peniston protocol. (Peniston & Kulkosky, 1989, 1990, 1991)

Reference		DISORDER	
Scott and Kaiser (Scott and Kaiser, 1998; Scott, Brod, Sideroff, Kaiser & Sagan, 2002; Scott, Kaiser, Othmer & Sideroff 2005)	NF protocols (SMR Beta training), followed by the Peniston protocol (alpha-theta training), in controlled study	stimulant abusing subjects with attention deficit type	with substantial improvement in program retention and long-term (12 months) abstinence rates.
Sokhadze, Stewart & Hollifield, 2007; Trudeau, 2000, 2005; Horrell et al., 2010; Peniston & Kulkosky, 1991; Peniston, 1994; Peniston & Kulkosky, 1995; Ross, 2013; Kaiser, Othmer & Scott, 1999; Bodehnamer & Callaway, 2004; Bodenhamer & BeBeus, 1995; Cowan, 1994; Fahrion, Walters,	increase in Beta/SMR waves	Alcohol	helped to take responsibility and to consider the seriousness of the job

Karch et al., 2015	**fMRI NF compared to the healthy control group**	**Alcohol addiction**	**managed to reduce neuronal activity at the anterior cingulate cortex, the insula, the inferior temporal gyrus and the medial frontal gyrus reduced the crisis of taking alcohol.**
Kirsch, Gruber, Ruf, Kiefer & Kirsch, 2015	**placebo controlled fMRI NF**	**ALCOHOL** 38 students who drink too much	Alcohol related cues produce **increased activation of reward** related brain regions like the **ventral striatum (VS) (neurobiological basis of craving); reducing the activation by NF Reduced craving.**
Ghosh, Jahan & Singh, 2014	NF	Alcohol dependence	increased cognitive skills while reducing anxiety and depression; abstained from being influenced by friends who drink alcohol

- The use of NF in the treatment of substance abuse (Rosenfeld, 1992),
- in opiate dependence (Dehghani-Arani, Rostami & Nadal, 2013; Arani, Rostami, Nostratabad, 2010)
- in heroin and cocaine addicts' desire for of substances (Heinz et al., 2006) and their treatments (Dehghani-Arani F, Rostami R & Nosratabadi, 2010),
- in Crack and Cocaine (Higgins et al., 1995) treatment (Burkett, Cummins, Dickson & Skolnick, 2004)
- the persistence of post-treatment effects of NF treatment of chemical abuse had been shown successful in patients treated with NF. (Bodehnamer & Callaway, 2004)

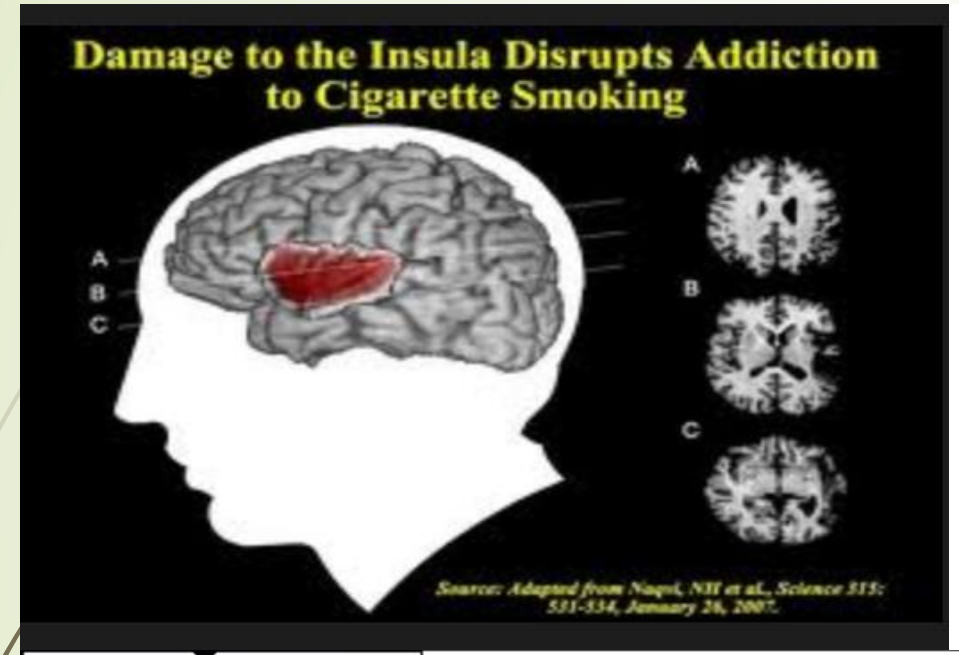
Burkett, Cummins, Dickson & Skolnick, 2005)	added NF treatment to inpatient treatment programs	CRACK COCAINE ADDICTS (n: 270)	Treatment increased 3 times the length of stay in the treatment center. In one year follow-up, 95.7 % of the 94 people who completed the treatment maintained a residence at home; 93.6 % were employed at work or school; 88.3 % had no other arrests; 53.2 % did not use alcohol and drugs; and 23.4 % reported using alcohol or drugs only 3 times, which was confirmed by urine testing.

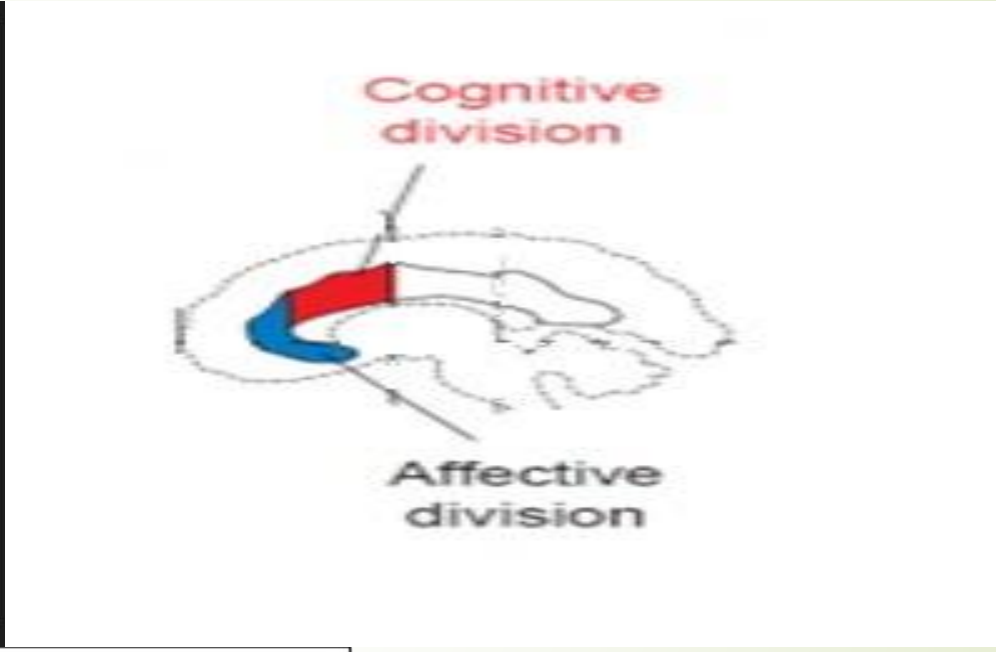
Arani, Rostami & Nostratabadi (2010)	**Controlled NF training** Matched subgroups received either NF training with medicine **(methadone/ boprenorphin maintenance therapy) or** just medicine.	**OPIOID DEPENDENCE** (detoxified patients with)	**The NF group showed significant improvements in output scales** **(hypochondriasis, obsessiveness, interpersonal sensitivity, aggression, psychosis, expectation of positive outcome and desire to use drugs), and QEEG.**
Horrell et al., 2010	NF treatment cocaine abusers		decreased self-reports on depression and stress scores, and urine tests collaborated reports of decreased use of cocaine and marijuana.

Keith, Rapgay, Theodore, Schwartz & Ross, 2015	**RCT clinician guided NF, SMR-theta NF and 3rd groups as normal therapy.**	**DRUG ADDICTS** **(n:95)**	**In the TOVA test, there was a significant improvement with an increase in attention with clinician guided NF**
Karch et al., 2015	sham controlled rtfMRI NF, compared to healthy controls.	ALCOHOL ADDICTION	Significant reduction of neuronal activity in the brain regions used as a target area for the NF-training (e.g. ACC, DLPFC, insula) during cue-induced craving in alcohol patients. ROI-based functional responses did not change significantly in healthy controls.

Insula/Anterior Cingulate

Schizophrenia,Obsesif Kompulsif Bozukluk/Cigarette addiction (Surmeli et al, 2011, 2012,2014)





http://www.psychological-opinions.gr/en/content/quit-smoking-new-approach

- Many smokers find it difficult to quit.
- Even after quitting, the relapse rate is high due to the **cravings** they experience.
- The reason for this difficulty in quitting and the high relapse rate appears to be due to **long-term changes in specific neural subsystems within the brain.**

- The anterior cingulate cortex (ACC) is a part of the brain's limbic system.
- According to functional imaging studies show that areas such as the **cingulated cortex**, the **anterior cingulate cortex**, the **orbitofrontal cortex**, and the **insula** activate in the presence of **drug-associated cures.**
- The insula is particularly interesting due to its potential role **in conscious urges**.
- **Damage to the insula may lead to a loss of the urge to smoke**

- 70% of smokers report wanting to quit, only 5% report being able to do so.
- **The relapse rate is more than 70%.**
- Craving and smoking cessation outcomes and has been linked with ACC activation during exposure to smoking cues.
- Studies using EEG neurofeedback were shown to have positive effects on drug use, treatment compliance, and **cue reactivity** in patients with **cocaine and alcohol dependence**.(Scott et al.,2005)

- By using neurofeedback (NF) from the anterior cingulated cortex (ACC), a key craving region, Cantebery et al.,2013, were able to reduce craving related to brain activation and self-reported craving in one visit.
- **Many controlled fMRI NF studies Show 76% success rate in quiting smoking.** (Li X et al.,2013; Hartwell et al.,2013)

- THANK YOU FOR LISTENING.