

Epigenetics and Neuroplasticity

The future of mental health

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Disclosures

- I have four books in this field that I receive royalties from:
- Handbook of Complementary and Alternative Therapies in Mental Health
- Please Don't Label My Child
- Mental Health for the Whole Child
- Parenting the Whole Child
- No other financial relationships or conflicts



Objectives

- Understand the nature of epigenetic influences on mental health
- Recall the most effective tools for epigenetic modification
- Be able to describe the benefits of Neurofeedback

agenda

- Overview
- Epigenetics
- Neuroplasticity
- Trauma

- closure

Medications in Psychiatry:

- 1. Reliable and effective for almost all
- 2. Generally very helpful, some minor limitations
- 3. Limited responses and frustrating for many
- 4. Grave concerns and limitations

Diagnosis in Psychiatry

- 1. Sophisticated and very reliable
- 2. Reasonable, reliable and most often adequate
- 3. Inconsistent and not very scientific
- 4. Comes down to opinion and judgment

From: **Self-blame–Selective Hyperconnectivity Between Anterior Temporal and Subgenual Cortices and Prediction of Recurrent Depressive Episodes**

JAMA Psychiatry. Published online October 07, 2015.1-8 doi:10.1001/jamapsychiatry.2015.1813

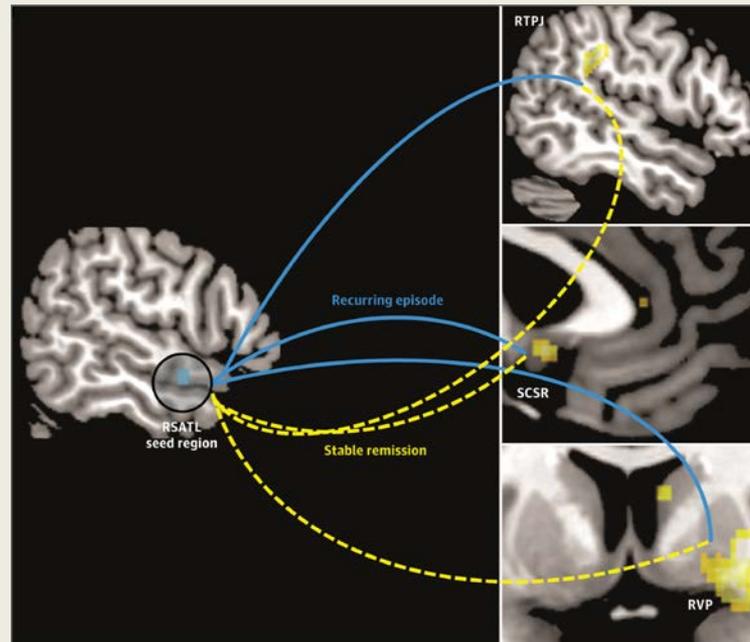
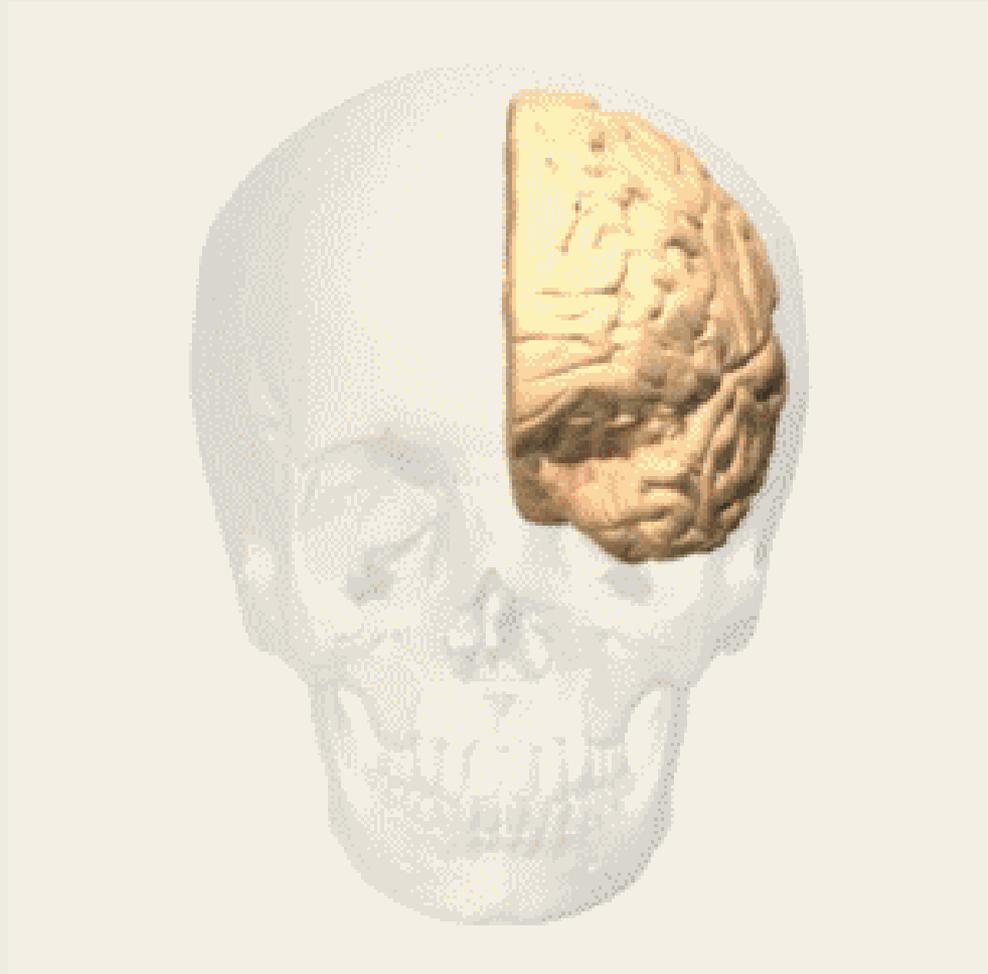


Figure Legend:

Regions Showing Functional Connectivity Group Differences With the Right Superior Anterior Temporal Lobe (RSATL) Seed Region for Self-blaming vs Other-Blaming Emotions Between the Recurring Episode Major Depressive Disorder (MDD) Group and the Stable Remission MDD Group Cropped images are displayed at an uncorrected voxel-level threshold of $P = .005$, with no cluster-size

Subgenual Cingulate



By 3D brain data is from Anatomography.

From: **Association of Thalamic Dysconnectivity and Conversion to Psychosis in Youth and Young Adults at Elevated Clinical Risk**

JAMA Psychiatry. Published online August 12, 2015. doi:10.1001/jamapsychiatry.2015.0566

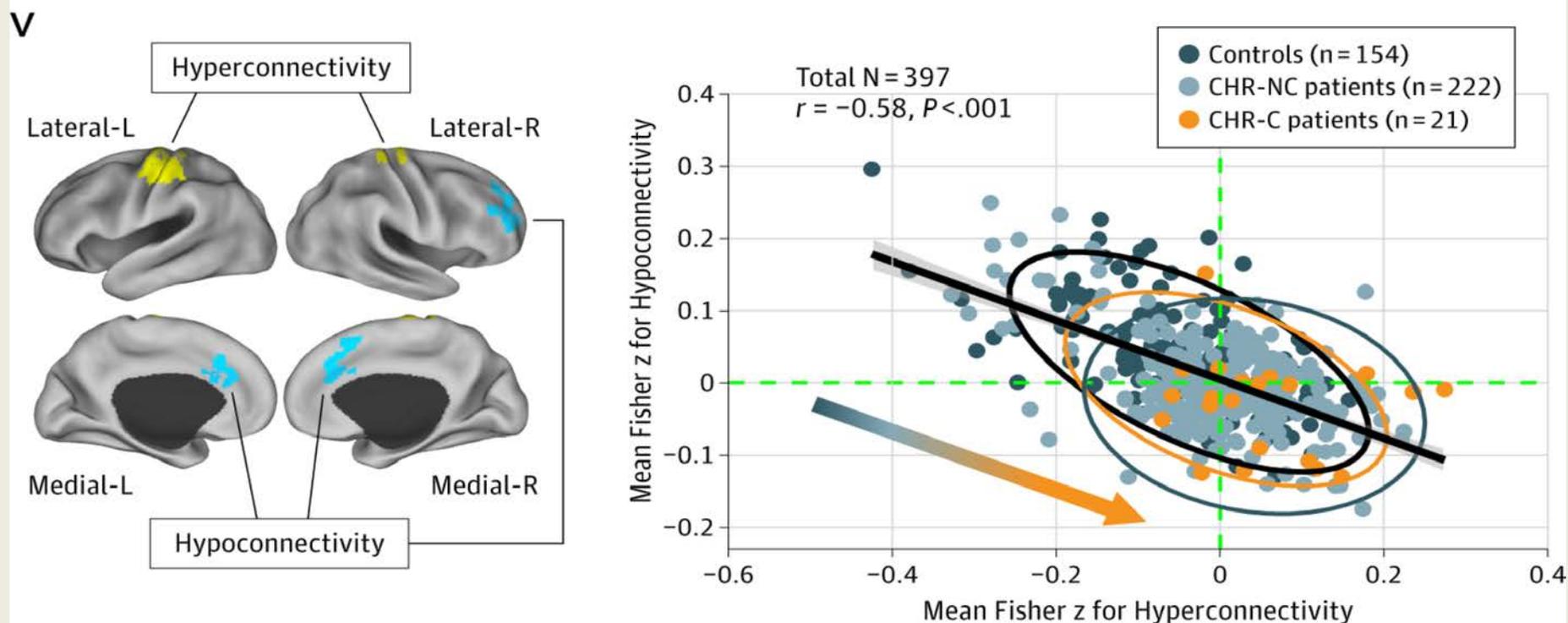


Figure Legend:

Association Between Thalamic Hyperconnectivity and Hypoconnectivity Across Study Participants Regions with reduced (blue) and increased (yellow) thalamic connectivity (Figure 1). A significant negative association is evident across all participants, collapsing across all 3 samples ($r = -0.58, P < 4.1 \times 10^{-38}$). Vertical/horizontal green dashed lines mark the zero points. Patients with clinical high risk of psychosis (CHR) who converted to full-blown illness (CHR-C) had a shift across the zero lines, indicative of weaker prefrontal-cerebellar-thalamic connectivity but stronger sensory-motor-thalamic connectivity. Patients with CHR who did not convert (CHR-NC) had a more intermediate degree of disruption, suggesting a gradient.

Genetics and Psychiatry

- Most illnesses are influenced by genetic factors
- The largest international dataset of ADHD, bipolar, depression, autism and schizophrenia found the variation from SNPs explained 17% to 29% of the variance in liability.
- Points to dimensional model with no separation between well and sick for depression and ADHD.
- “ADHD lies on the spectrum of normal trait variation.”

Stergiakouli, E *JAACAP* 2015 54 (4): 322

Lee, SH *Nat Genet.* 2013 45: 984-994



GAME CHANGERS IN MODERN NEUROSCIENCE

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Neuroplasticity

Epigenetics

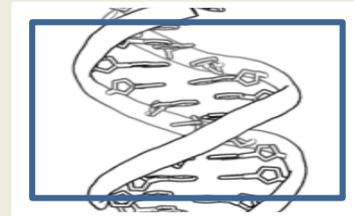
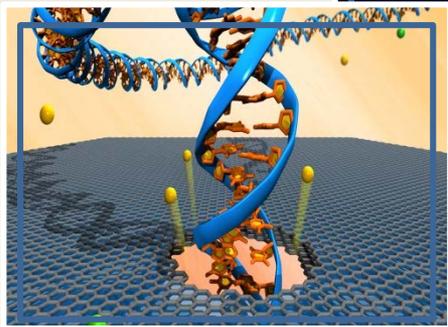
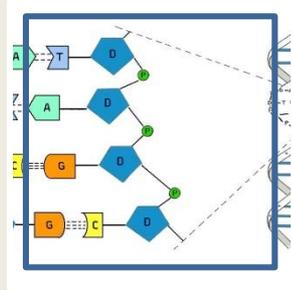
DNA of Human Genome



■ Junk DNA (97-98%)

■ Protein Synthesis DNA
(2-3%)

Epigenetics



Epigenetics

New Definition from NIH:

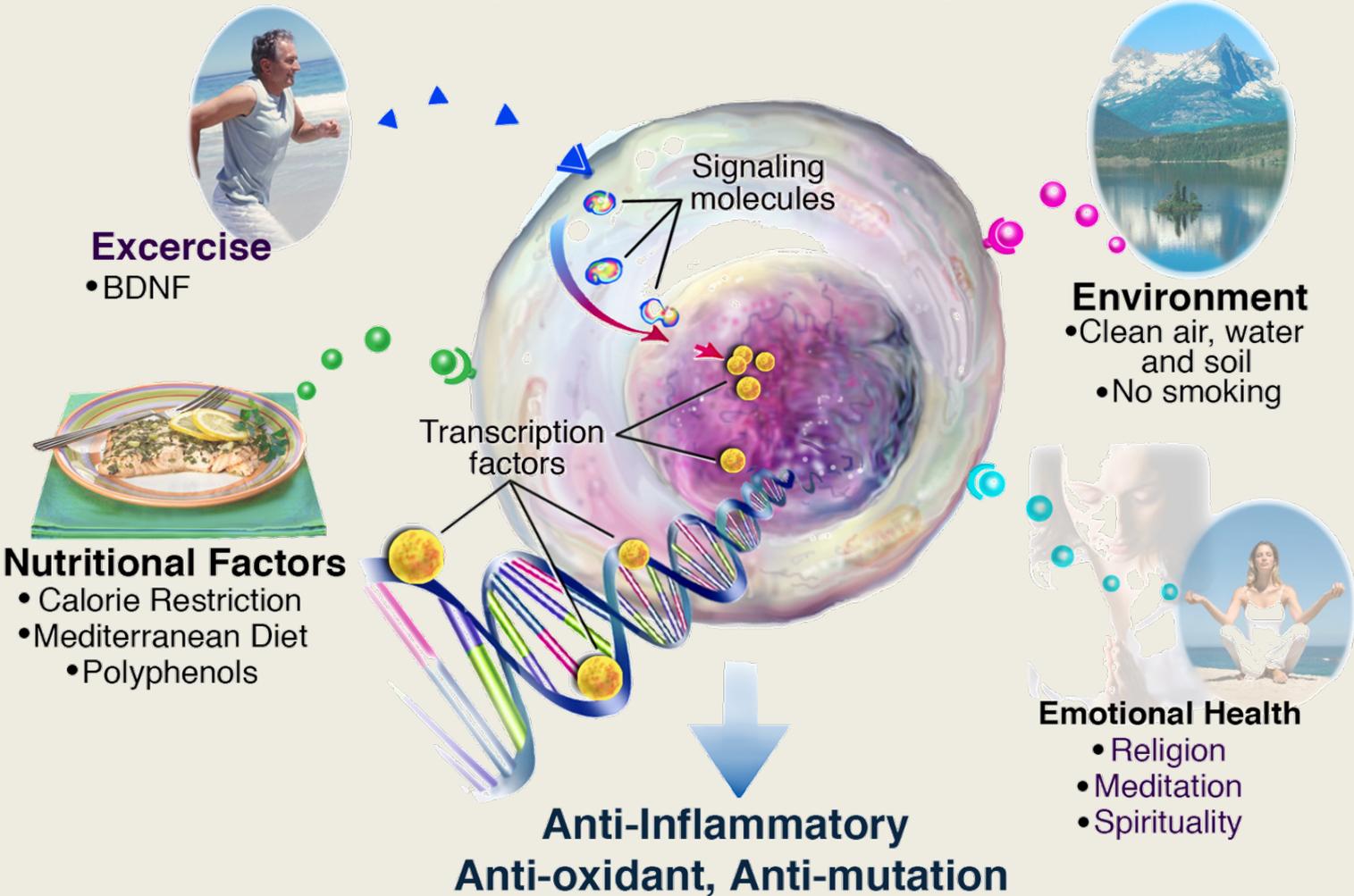
“Includes both heritable changes in gene activity and expression but also stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable.”



ENCODE

- Selected only 1% of the human genome to study
- The human genome is pervasively transcribed
- Over 80% of human DNA involved in transcription
- 3 million plus sites exist for external influence
- 3 dimensional influence may exist in genome
- The interactive and epigenetic nature of the human genome far exceeds previous thought

Epigenetics and Gene Activation for Improved Health and Longevity



Epigenetics: Most Studied

- Diet
- Smoking
- Infections
- Starvation/wasting
- Environmental influences (endocrine disruptors)
- Child Care

Examples

epigenetics at play



Gut Microbiota Modulates Brain Development

- 5 different brain regions, found nearly 40 genes that were affected by presence of gut bacteria.
 - These affected nerve cells and influenced genes to be turned off or turned on
 - Germ free mice were hyperactive and disinhibited
 - Life long changes from early alteration

Diaz Heijtz R, *PNAS*, 2011 108 (7): 3047-52

Epigenetics in Suicide and Depression

- Meta analysis of 16 relevant studies
- 14/16 studies found significant association between epigenetic changes and S/D
- Hypermethylation of BDNF (Brain Derived Neurotrophic Factor) involved in suicide
- trkB Hypermethylation of Brodman 8 and 9 involved in suicide.

Lockman, LE et al *Psychiatry Res* 2015 June 27 1781 (15): 383



Anti-Depressants: new mechanism?

- Paroxetine found to induce epigenetic changes
- Alters DNA methylation
- Shifts glucocorticoid receptor involved in stress response via FKBP51
- FKBP51 gene expression linked to BDNF
- First study to link epigenetics of stress and meds

N.C. Gassen et al., *Science Signaling*, doi:10.1126/scisignal.aac7695, 2015.

Endocrine Disruptors (ED)

Xenobiotics that alter the epigenome:

- May shift entire endocrine axis
- Interfere with normal sexual development
- Can last generations
- Operate at much different concentrations than typical chemical reactions

Casati L. *Endocrine Disruptors* 2013; 1, 4 10.4161/endo.27347

Methoxychlor (MXC)

- Organochlorine pesticide
- Actively metabolized: potent estrogenic effect on epigenome
- Creates epimutations
- Alters estrogenic development in all cell lines
- Effect lasts **four** generations

Casati L. *Endocrine Disruptors* 2013; 1, 4 10.4161/endo.27347



Mercury Exposure

- Meta analysis of studies prior to 4/2014
- No link found with vaccines/ thimerosal

Clear link with environmental exposures:

- Significant link with ADHD (OR 1.66)
- Significant link with ASD (Autism Spectrum disorder) (OR 1.60)

Yoshimasu, K et al *Neurotoxicology* 2014 September 44: 121-31.



Epigenetics *cont.*

female yellow mouse (agouti gene unmethylated and active)

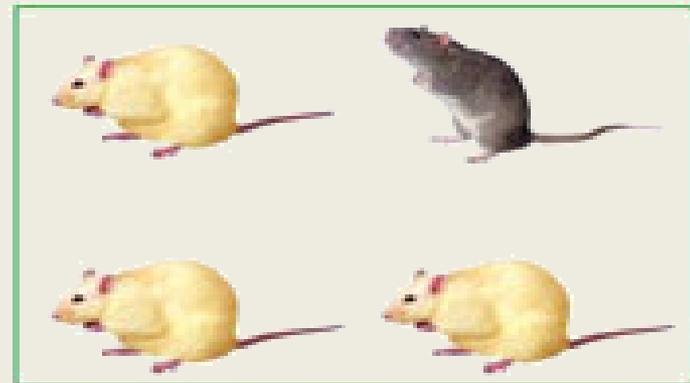


diet supplement during pregnancy and nursing with additional methyl groups

no dietary supplementation



Offspring mostly brown and healthy; agouti gene methylated and silenced



Offspring mostly yellow and unhealthy; agouti gene unmethylated and active



OPINION

Open Access

Preventing mental health problems in offspring by targeting dietary intake of pregnant women

Adrienne O'Neil^{1,2*}, Catherine Itsiopoulos³, Helen Skouteris⁴, Rachelle S Opie³, Skye McPhie⁴, Briony Hill⁴ and Felice N Jacka^{1,5,6,7}

Abstract

Background: The concept of 'early life programming' considers the importance of very early environmental exposures throughout the gestational period on the subsequent health outcomes of offspring. The role of maternal dietary intake, specifically, has been highlighted after recent studies have shown maternal diet quality to predict mental health problems in offspring. Even in the pre-conception period, maternal nutrition can have permanent

The Effect of Diet Years Later

- Maternal diet linked to persistent epigenetic changes in infants
- Paternal diet may be important
- Maternal diet linked to later behavioral issues
- Whole foods better than supplementation

O'Neil, A et al *BMC Medicine* 2014 12: 208

Neuroplasticity

changes who we are



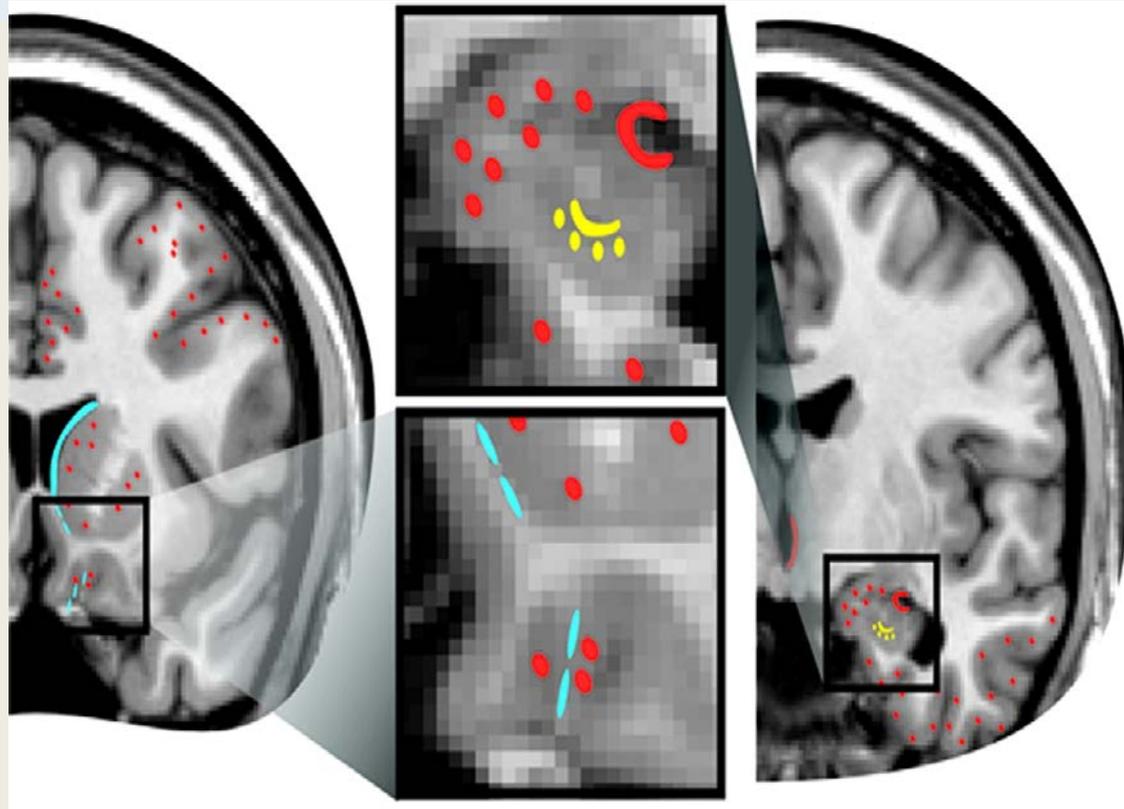
Neuroplasticity

Includes:

- New cells (neurons, glial cells)- neurogenesis
- New connections-synapses, dendrites
- Axonal sprouting
- Pruning

From: The Dynamic Brain: Neuroplasticity and Mental Health

The Journal of Neuropsychiatry and Clinical Neurosciences



Cover and FIGURE 1. It is now generally accepted that adult neurogenesis occurs in all mammals, including humans. Neurons born in the subventricular zone adjacent to the caudate (solid blue area) migrate ventrally, then rostrally (blue dashes), to be incorporated into the olfactory bulb. Neurons born in the subgranular zone of the dentate gyrus (solid yellow area) are incorporated into the dentate gyrus (yellow dots).

Change in the Brain

Growth factors:

- Brain-Derived Neurotrophic Factor (BDNF)
- Vascular Endothelial Growth Factor (VEGF)
- Insulin-like Growth Factor (IGF)

These increase the rate of cell birth and promote maturation and survival. Glial cells are now seen to play a critical role as well.

Cognition and Brain Size

- 127 adults with mild cognitive impairment
- Intensive multi-disciplinary brain fitness program
- 12 week program: 5 hours per week
- Q-EEG, MRI, neurocognitive tests: pre and post
- Coaching on exercise, cognitive skills, diet, supplementation (omega 3 EFAs), mindfulness
- 2 hours per week of Neurofeedback

Fotuhi, M *Alzheimer's Association International Conference (AAIC) 2015. Abstract 4331. Presented July 19, 2015.*



Cognition and Brain Size

- 84% demonstrated significant improvement in 3 of 10 components on cognitive testing ($p < .05$)
- Post study MRI: 65% improvements in hippocampal growth above baseline
- **Crucial proof of concept**

Fotuhi, M *Alzheimer's Association International Conference (AAIC)* 2015. Abstract 4331. Presented July 19, 2015.



The Q EEG & Neurofeedback

The essence of neuroplasticity

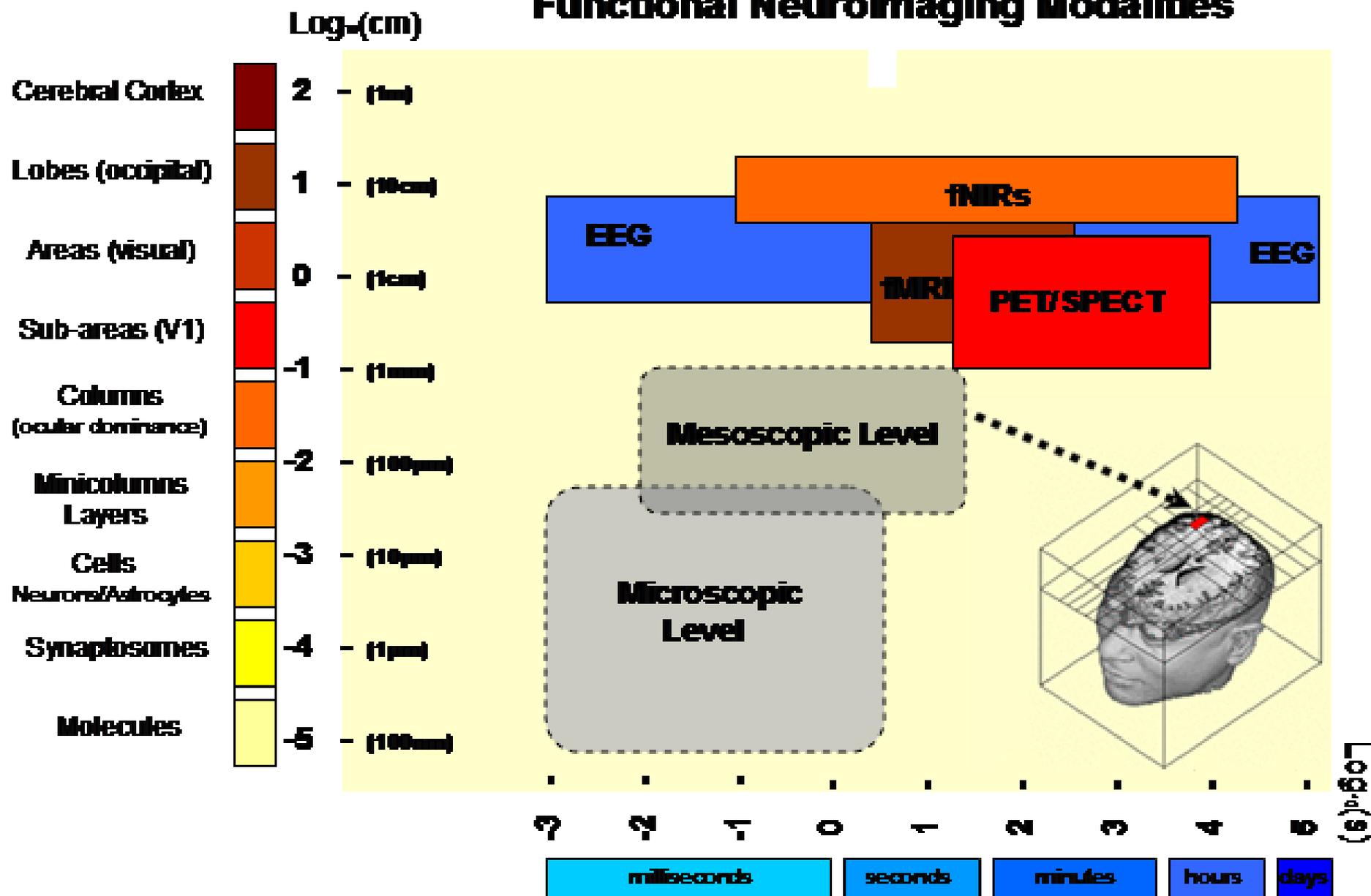


Electrical Neuroimaging – Assessment and Treatment

Advantages of Electrical Neuroimaging:

- 1. Spatial Resolution – 1 cm to 3 cm**
- 2. Temporal Resolution – 1 msec**
- 3. Imaging of Current Sources**
- 4. Imaging of Network Connections**
- 5. Integration with DTI & fMRI (Brodmann Areas)**
- 6. Inexpensive (\$10,000 vs \$3,000,000)**
- 7. Dry Electrodes & Wireless Caps**
- 8. Portable**
- 9. Integration with Smart Phones & Tablets**
- 10. Can Assess & Treat in Real-Time¹**

Functional Neuroimaging Modalities



Studies on ADHD for Neurofeedback

Since 2009, there are now a total of eight **RCT** (**Randomized Controlled Trials**) studies (Linden, et al, 1996, Levesque, et al, 2006, Leins, et al, 2007, Gevensleben, et al, 2009, Holtman, et al, 2009, 2010, Steiner, et al, 2011, Bakhshayesh, et al, 2011, Meisel, et al, 2013)

All demonstrated significant improvements in attention, hyperactivity or impulsivity as compared to controls.



Long Term Effects-NF

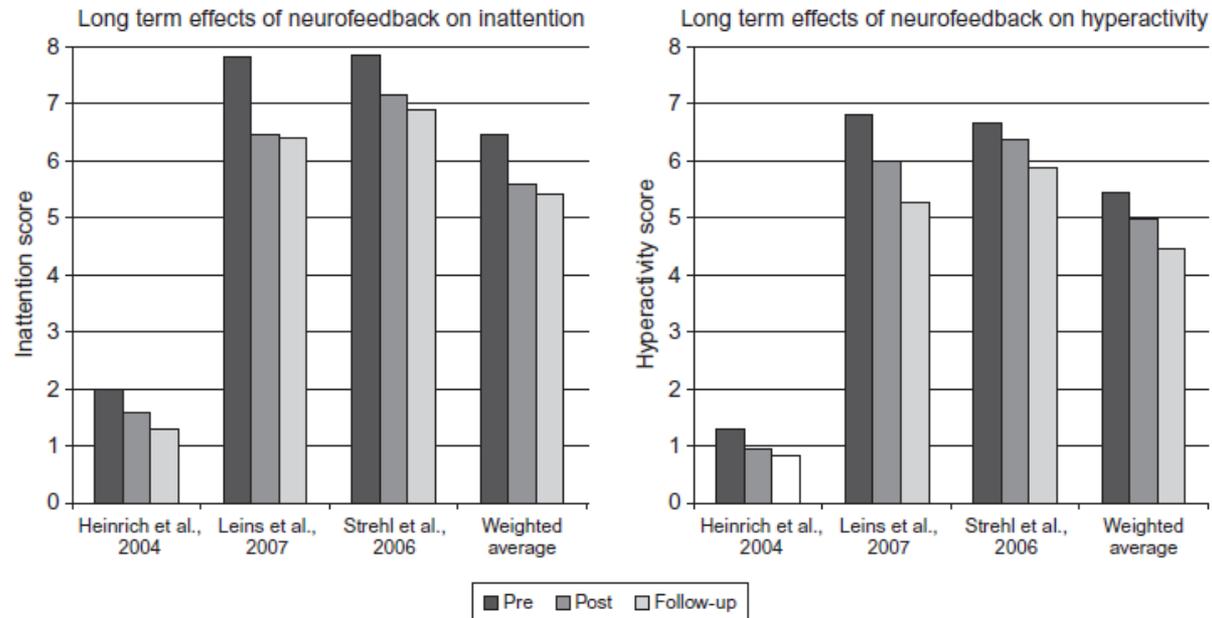


Figure 15.1 The effects of neurofeedback over time for three controlled studies for inattention (left) and hyperactivity (right). The study by Heinrich et al. performed 3 months follow-up and the other two studies performed 6 months follow-up. Note that the effects of neurofeedback tend to improve further over time (as opposed to the effects of medication, which are not sustained when the medication is stopped).

Enduring Effects of NF in Autism (75 cases) Follow up= 1 yr.

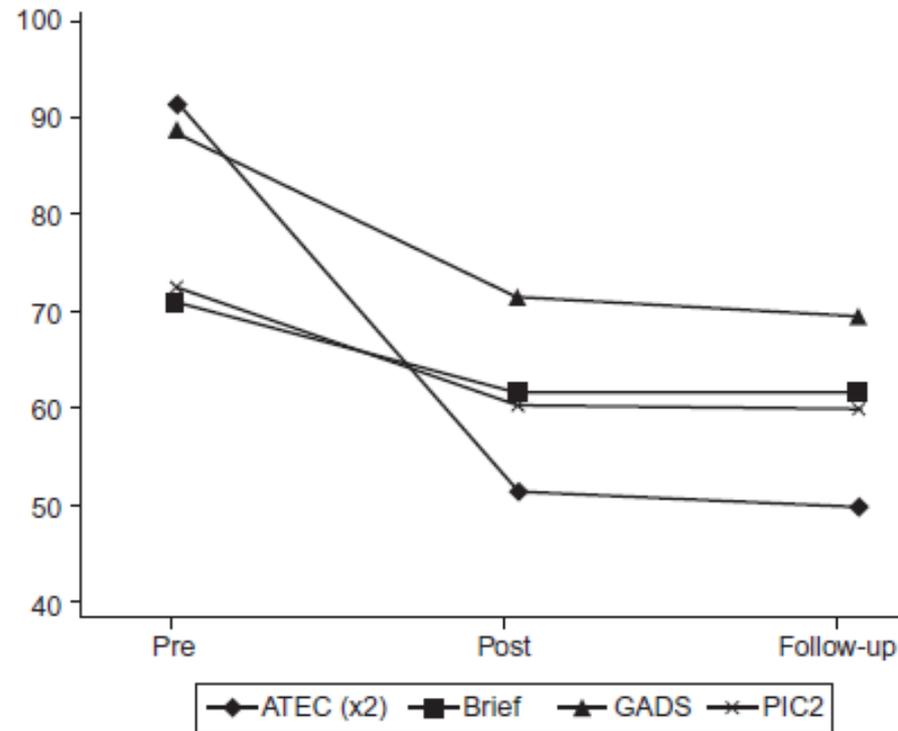
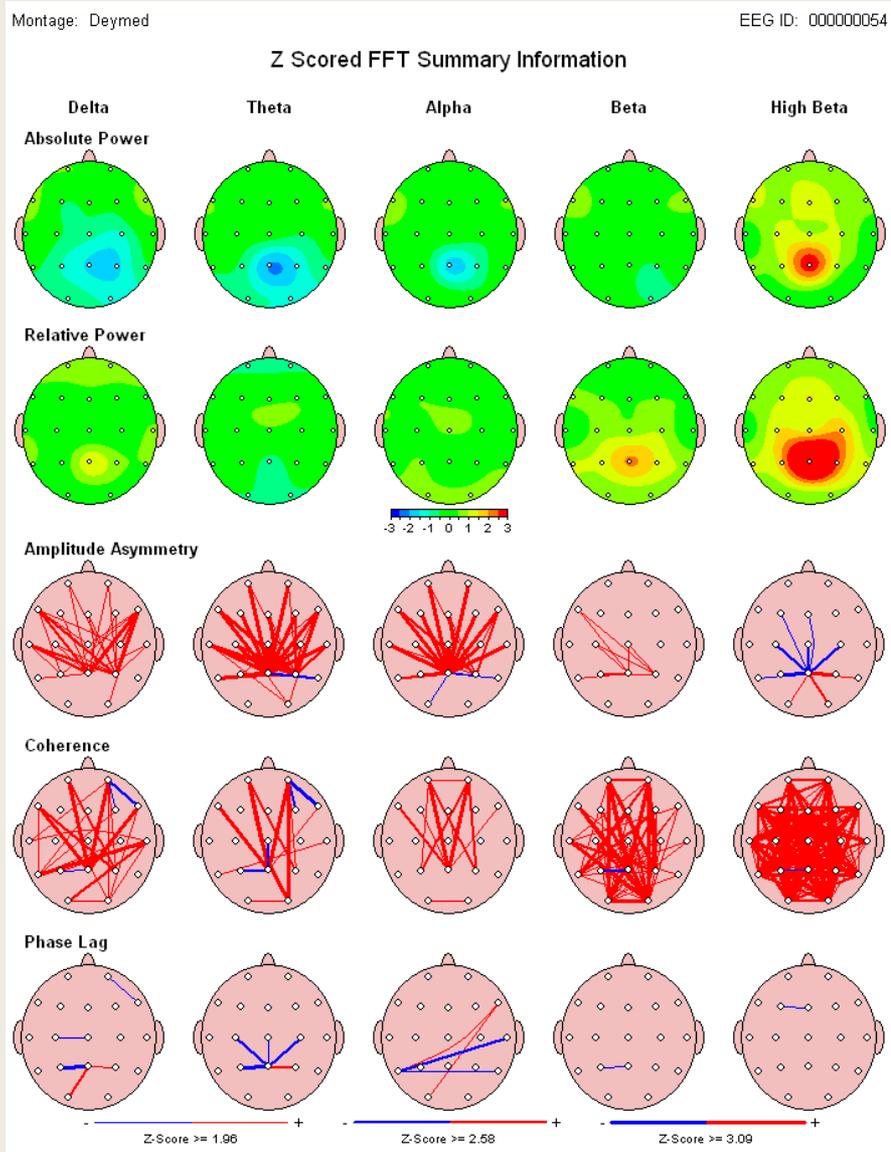


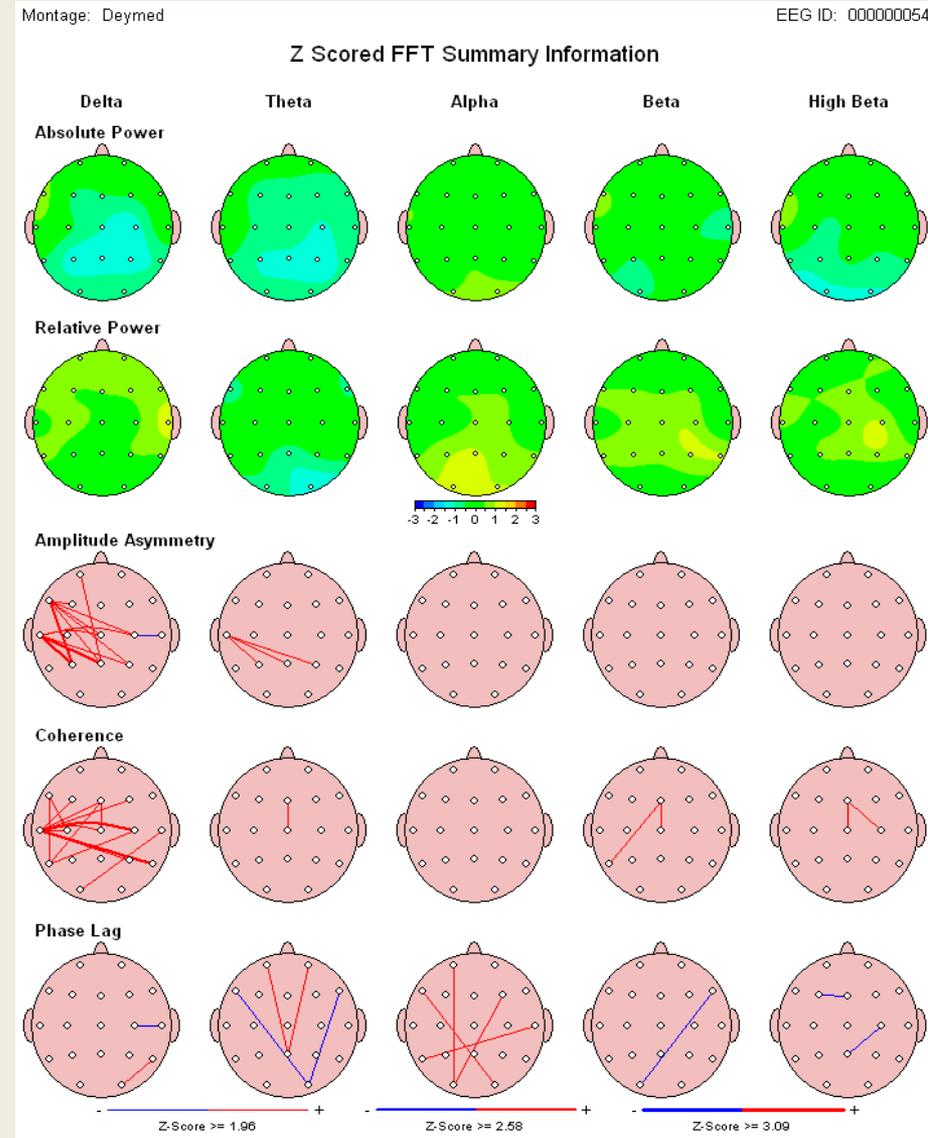
Figure 15.6 Clinical improvements among subjects as assessed by the parents rating scales of ATEC, BRIEF, GADS, and PIC-2 for pre-, post-treatment, and follow-up periods.

Examples of Surface EEG Changes After EEG Neurofeedback

Pre-Treatment-case #1



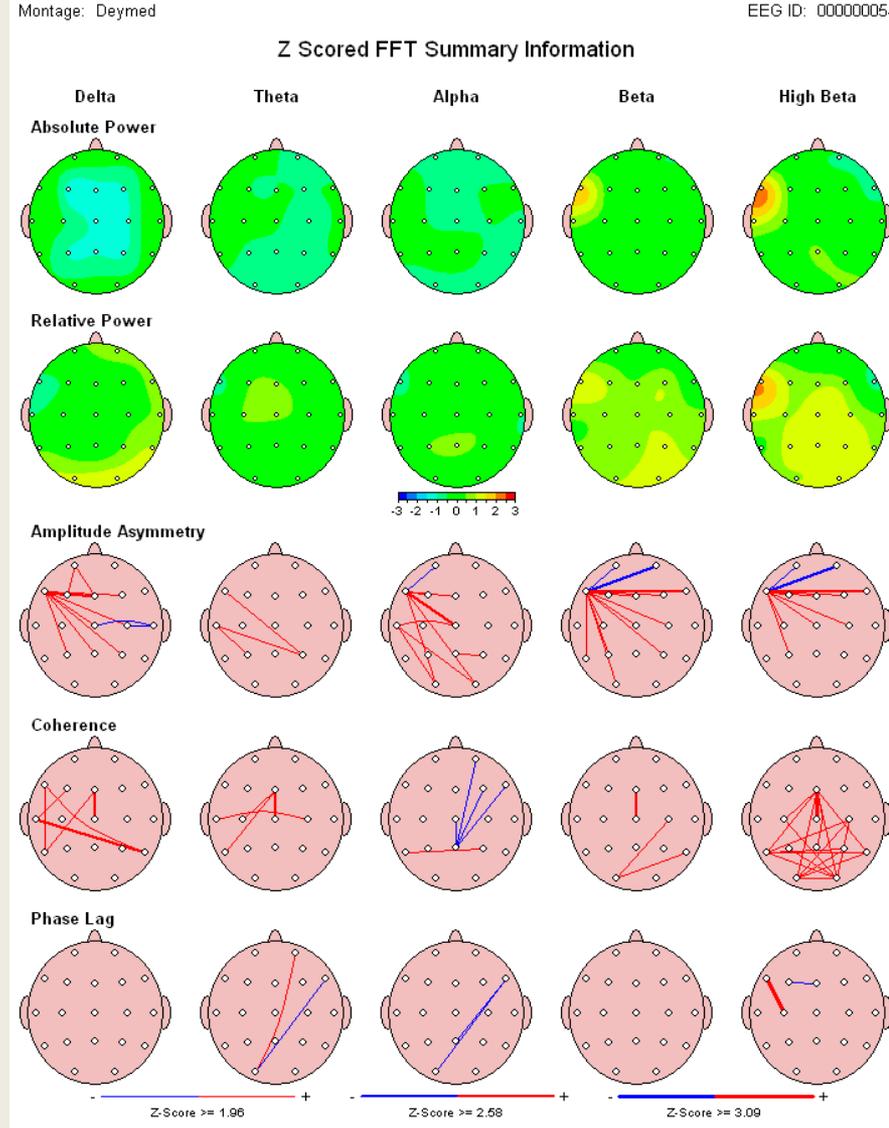
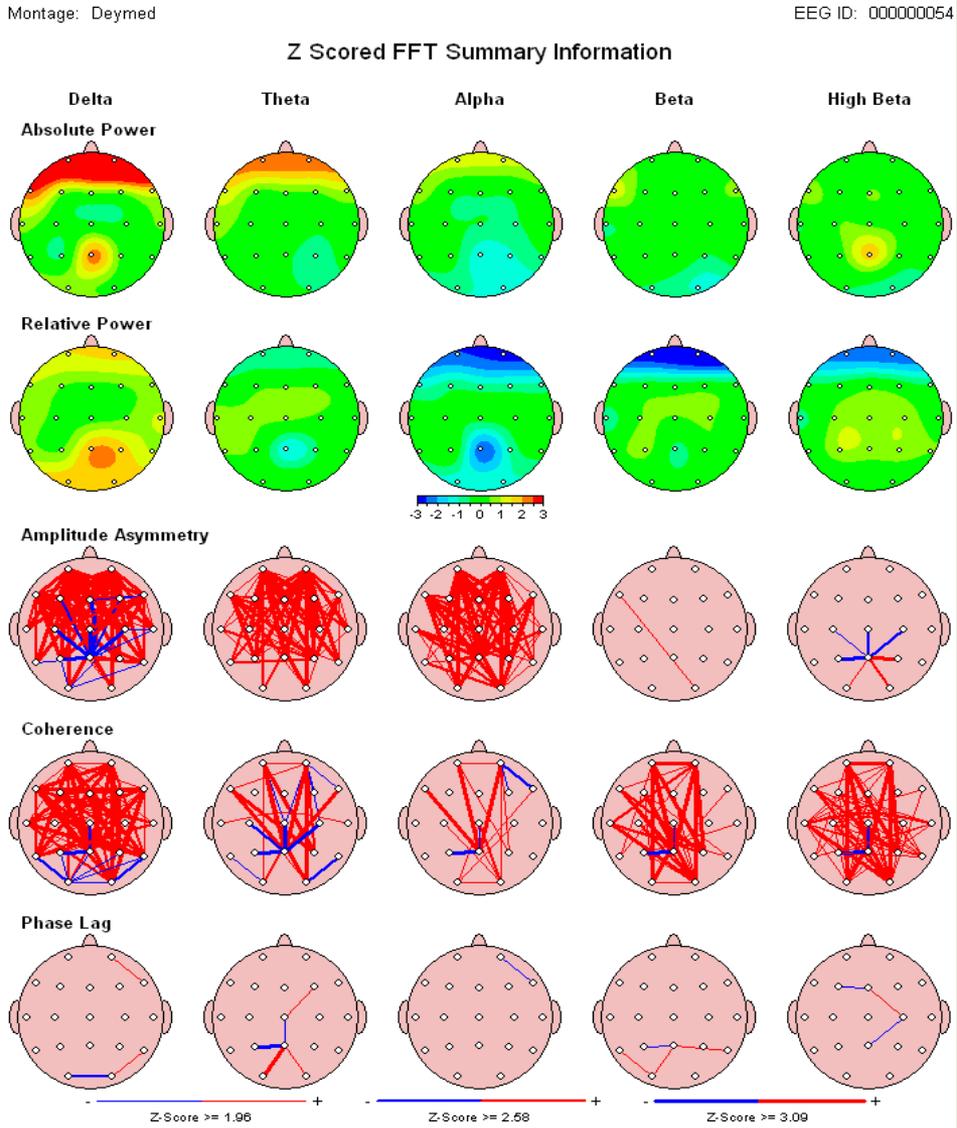
Post – 10 Treatments



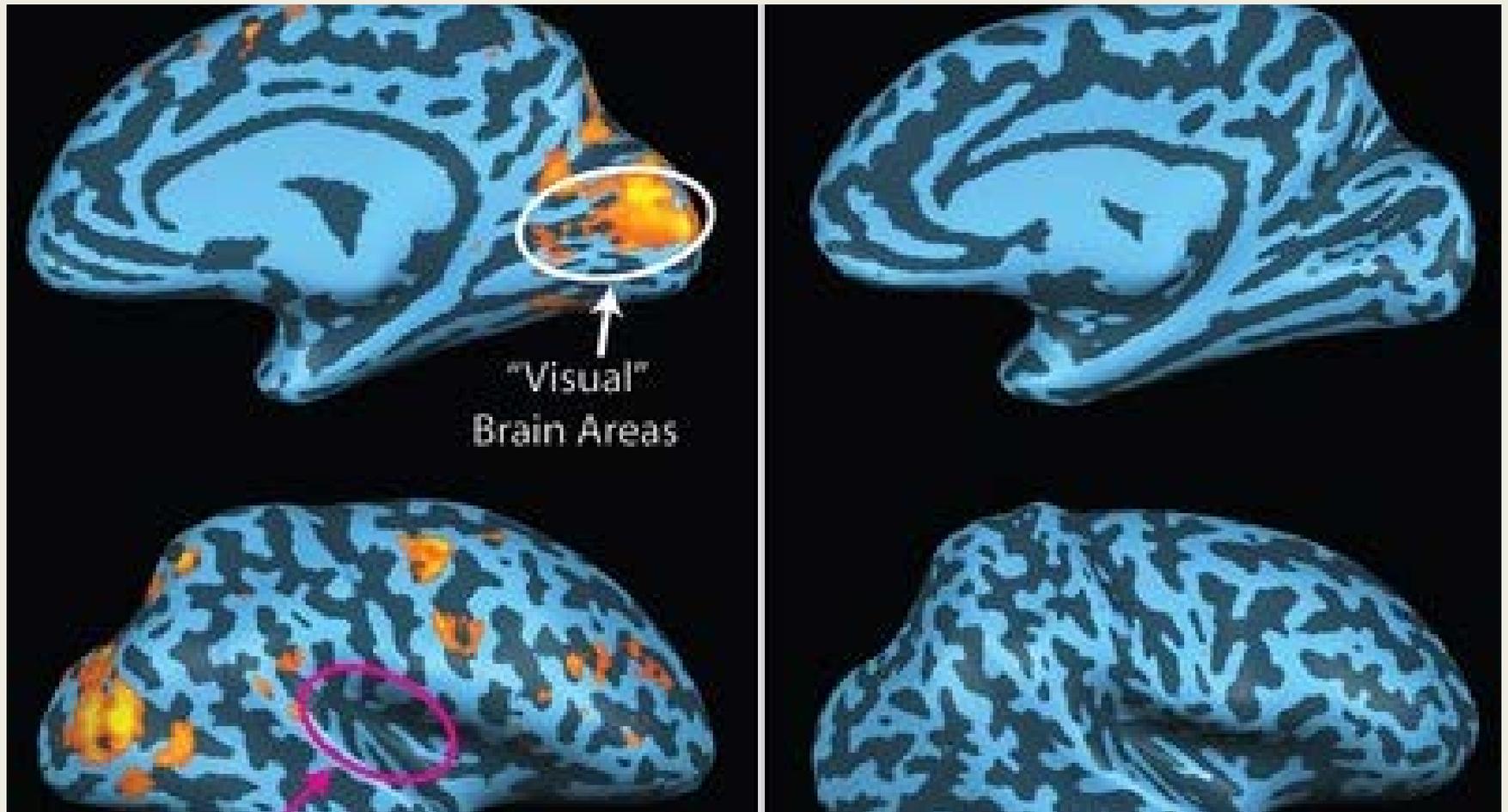
Examples of Surface EEG Changes After EEG Neurofeedback

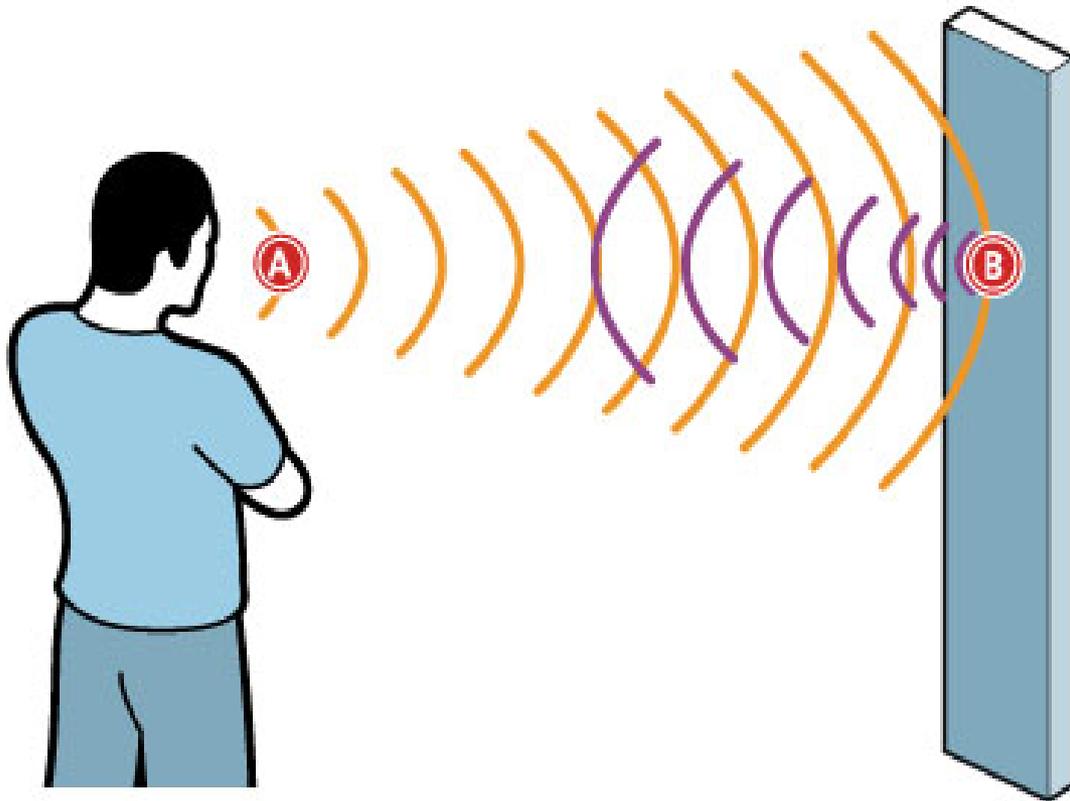
Pre-Treatment: case #2

Post – 10 Treatments



Human Echolocation

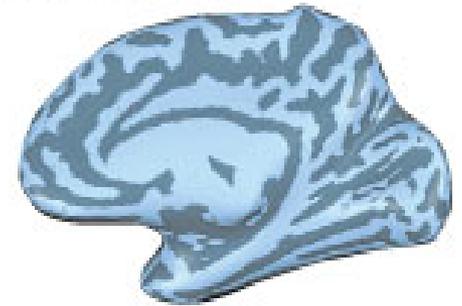




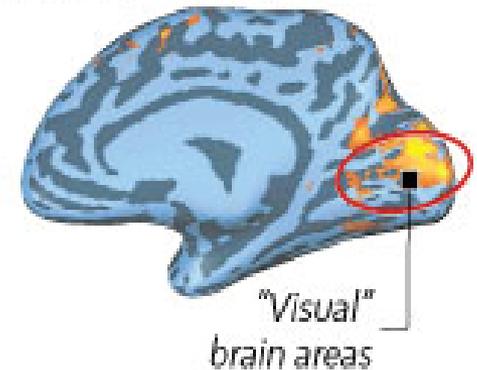
A The echolocator uses his tongue and mouth to create clicking sounds.

B Sound bounces off object. A practiced echolocator can identify objects around him by the echo, much like bats do.

Non-echolocator



Echolocation expert



C Sounds are played back to participants later during MRI scan. These scans show activity in areas of the brain that normally process visual information.

Trauma

A bad example

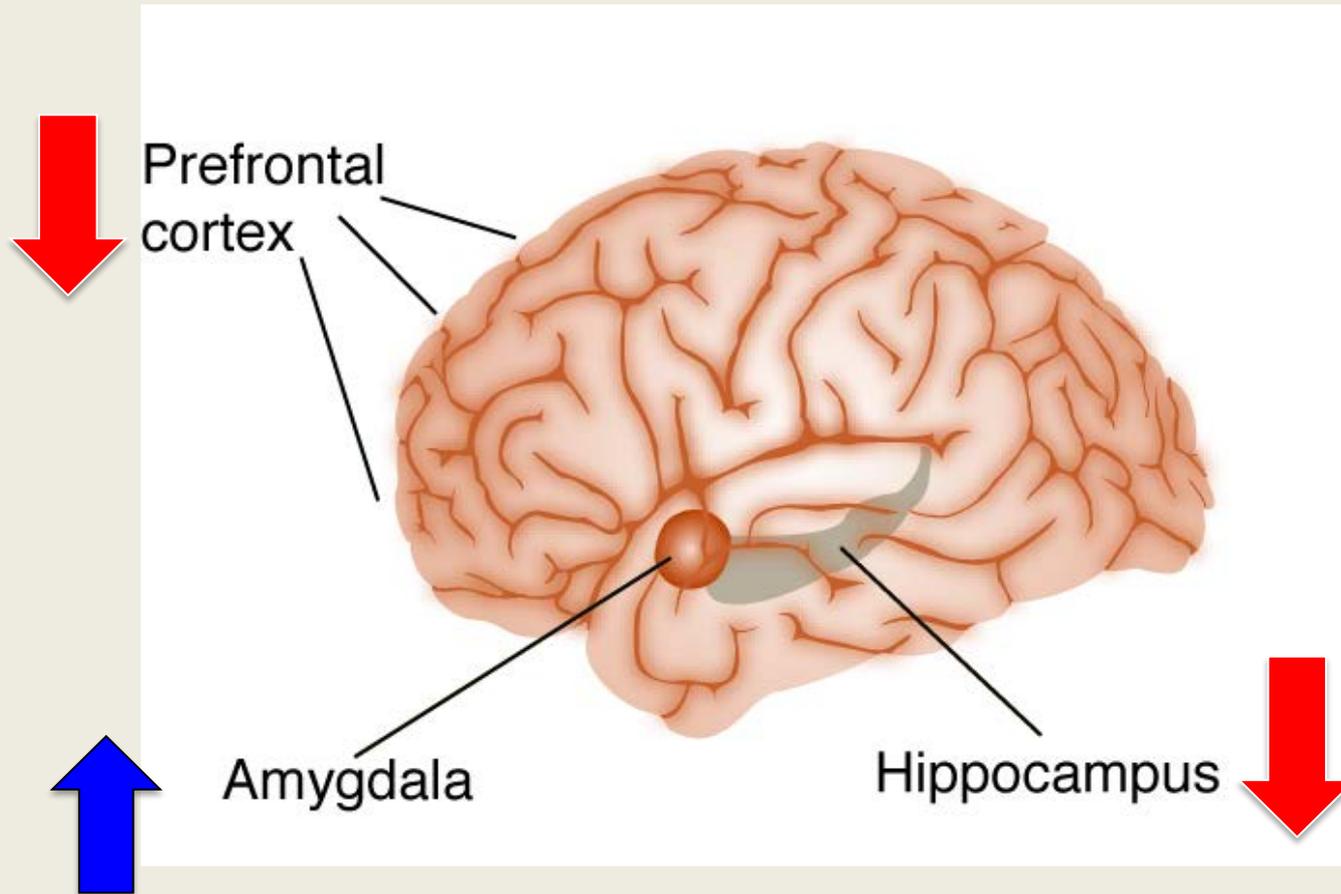


Three Brain Changes in PTSD

- **Amygdala:** Increased activation to normal stress
- **Prefrontal Cortex:** Less activation
- **Hippocampus:** Reduced volumes

“Neurocircuitry Model” of PTSD

- Deficit in extinction of fear conditioning



Adverse Childhood Experiences

- Surveyed 17,000 adult pts
- Experience of abuse, neglect, domestic violence, crime, alcoholism. 8 categories/10 questions.
- **ACEs correlate in graded fashion with every negative outcome in affective, somatic, memory, substance abuse, aggression and sexual disorders**

Felitti, V *Eur Arch Psychiatry Clin Neuroscience* 2006, 256 (3): 174-86

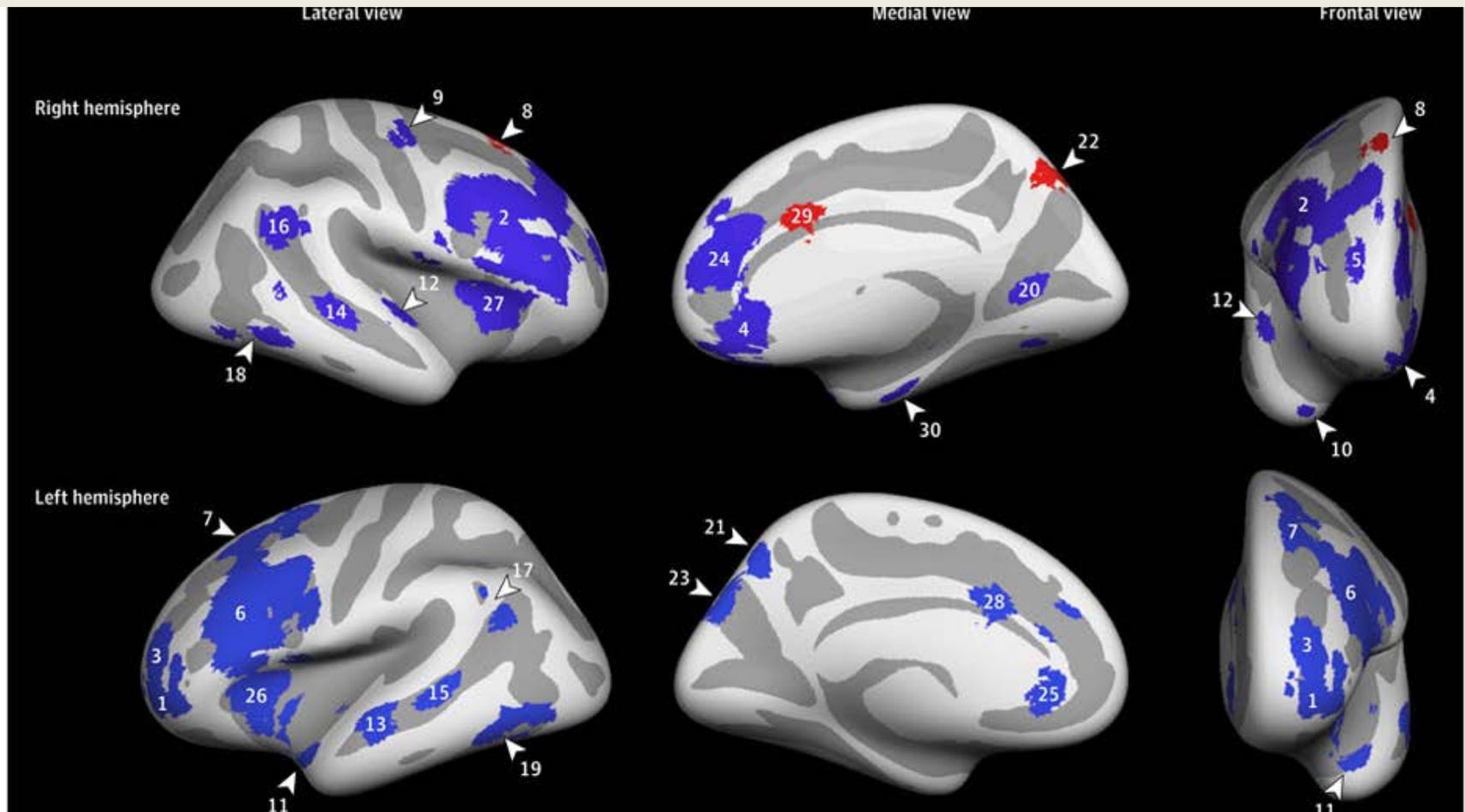


Abuse creates epigenetic change in HPA axis

- Post mortem study of suicide victim's brains
- Compared abuse survivors versus controls
- Structural changes in NR3C1 receptor vs controls
- NR3C1 responsible for deactivation of HPA axis
- Links to schizophrenia, mood disorders and suicide
- **Most research finds continuum of stress and abuse-**

McGowan, P *Nat Neuroscience* 2009, 12:342-348

Early Childhood Adversity Alters Brain Development 20 Years Later



Jensen, S et al JAMA Psychiatry 2015 online August 17th

From: **Multicenter, Double-blind Comparison of Sertraline and Placebo in the Treatment of Posttraumatic Stress Disorder**

Arch Gen Psychiatry. 2001;58(5):485-492. doi:10.1001/archpsyc.58.5.485

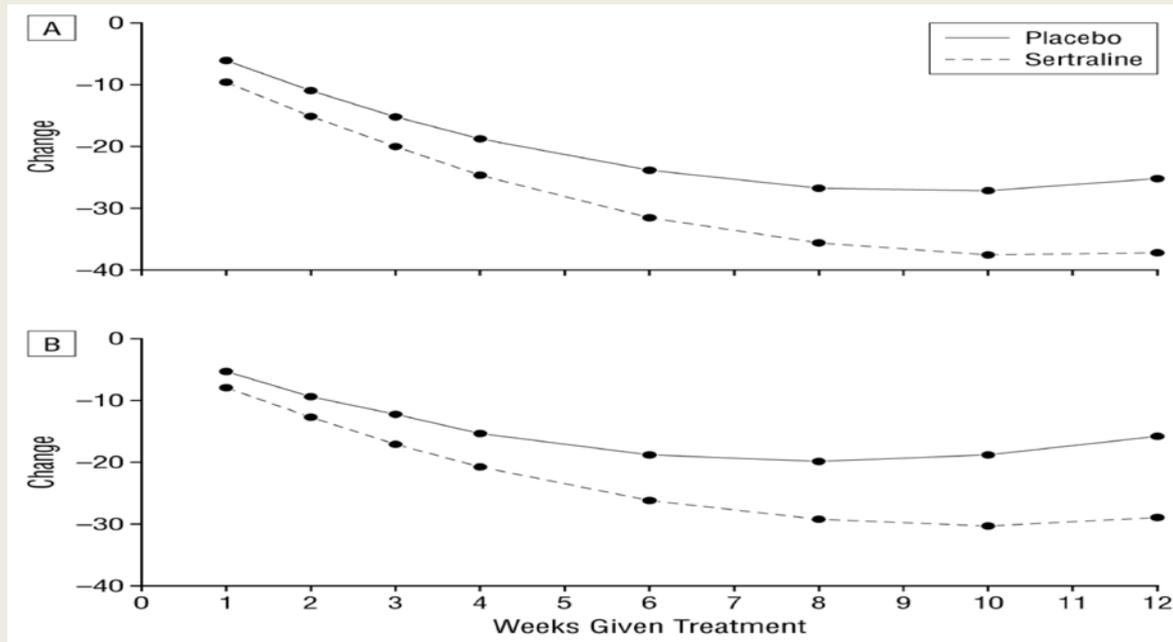


Figure Legend:

Results of random regression analyses comparing the effects of a 12-week treatment with sertraline and placebo. A, Mean change score estimate from a random regression analysis on part 2 of the Clinician-Administered Posttraumatic Stress Disorder Scale ($t_{1379} = -2.96$, $P = .003$). B, Mean change scores from a random regression analysis on the Impact of Event Scale ($t_{1377} = -3.45$, $P = .0006$).

Closure

Where are we?



Summary

- Psychiatry must accept epigenetics and neuroplasticity as foundational
- We must move to a ecological/systems oriented model that emphasizes the individual's power of change
- As we move to a model of health we will begin to emphasize empowering therapies rather than suppressive ones

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What we can do

- Work with patients on nutrition
- Eat organic (Clean15 and Dirty 12)
- Pay attention to toxic burden, test it
- Avoid high doses of meds
- Think about methylation
- Employ tools that empower change, such as NF, meditation, therapy, etc
- Exercise makes a difference
- Evaluate and support sleep

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