

CIM workshop

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- No disclosures

EEG Biofeedback or NeurofeedbaCK

- Since 1971 there have been over 1,143 peer reviewed human EEG biofeedback journal articles listed in the National Library of Medicine database and 4,623 journal articles using the search terms “Brain-Computer-Interface”.

History of NF

- Stermann, 1969
- Operational Conditioning with Cats-Cats were connected to EEG to record what happened during operational conditioning
- Traditional conditioning where a lever is pushed and food comes into a bowl=now cat presses lever when hungry.
- Next, a new element was introduced to the experiment: a tone. If the cat pressed the lever while the tone was on, the dose of chicken broth and milk would not be delivered
- .
- The cat had to wait for the tone to stop before it could press the lever and get the reward.
- Stermann observed that while the cat was waiting for the tone to stop, it entered a unique state of consciousness.
- It remained absolutely still, though extremely alert, anticipating when the tone would stop.

History of NF

- Accompanying this motor stillness , a specific rhythmic frequency of **12Hz to 15Hz** over a specific part of the brain was seen (which he called the **sensorimotor** frequency or **SMR**).
- Stermann wanted to see if he could teach the cat how to produce that specific frequency at will.
- No lever was used, instead, if the cat produced a half second of the SMR frequency, he were given a shot of the broth and milk.
- Cat would produce in anticipation of broth and milk
- Over time the cats learned how to produce the frequency at will.

History of NF-SMR

- Lubar-first to use NF on hyperkinetic child in 1976

Placed 2 electrodes at C3 and C4

Trained up Sensorimotor EEG rhythm= Beta
(12-14Hz) so (theta) 4-8 Hz was no longer present

qEEG was not utilized yet

Result-increased attention and decreased
seizures

Called Sensorimotor Rhythm (SMR)

Seizure study used ABA design

History NF

- Operant conditioning-
- NF can provide a reward for the appearance of a particular electrical event in the brain.
- The electrical pattern soon begins to appear in anticipation of the reward, leading to increased frequency of appearance of that electrical pattern.
- In a similar way in humans, a person focuses on a screen and if a dot appears on the screen during an NF session with each occurrence of a particular targeted EEG pattern or rhythm, the rhythm eventually continues to occur in anticipation of the dot appearing.

Types of Surface NF Protocols for ADHD

- **1. Sensorimotor Rhythm (SMR)**
- **2. Theta Beta Ratio (TBR)**
- **3. Slow Cortical Potential (SCP)-**
- Others NF techniques:
 - Infra Slow Fluctuation Training-new on the horizon (Smith)
 - Multivariate Coherence- (Coben) used in autism-mentioned later
 - Power/Ratio-used in athletes for high performance-(Sherlin)
 - Due to issues surrounding Low Energy Neurofeedback System (LENS), which uses passive radiofrequency electromagnetic stimulation with eyes closed, and Hemoencephalographic Neurofeedback (HEG), which provides feedback about cerebral blood flow, these techniques will not be reviewed here due to limited space and time.

Studies on ADHD-

1. Meta-analysis of 15 (1194 youth) randomized controlled studies using SMR, TBR or SCP (Arns, et al, 2009, Hurt, et al, 2014)-

None in metaanalysis used qEEG

Six studies included randomization and 3 non-randomized studies compared NF to Medication

In all studies, only 12% were on medication

Mean ES for measures of inattention was 0.72, hyperactivity/impulsivity 0.70, all ADHD symptoms 0.62, and all problems (ADHD or otherwise) 0.57.

Meta-analysis of NF on ADHD-

- Of the six RCT studies, the ES size was 0.54
- However, none of these studies used qEEG
- Arns, 2002

Lubar-1st to use qEEG

- Began using qEEG to differentiate ADHD from NI (1991)
- ADHD individuals with excess theta (4-8 HZ) and decreased Beta (13-30 HZ) at Fz, FCz or Cz
- Trained down theta and trained up beta at C3 and C4
- Lubar called this the Theta/Beta protocol or Ratio (TBR)

(Arns, Conners and Kraemert, 2012)

(Linden, et al, 1996)

First to use TBR for ADHD with qEEG in comparison to wait list

Result-increased attention and decreased impulsivity

PERSONALIZED MEDICINE-Use of qEEG for Treatment Matching

- Use of qEEG to determine subtypes:
- A. Used to determine specific protocol to be used with NF
- B. Used to determine who will respond to medicines
- C. In line with NIMH new Directive-Research Domain Criteria (RDoC) under the sub-analysis of circuits

Use of qEEG subtypes-to determine NF protocols

- B. NF protocols using qEEG.
- Arns (2012)- Based on qEEG data one of 5 NF protocols selected:
 1. *Frontocentral Theta/Beta* protocol- when excess theta was observed midline site at FZ, FCz or Cz where activity was maximal using Z scores, Theta dec/Beta inc protocol was used unless:
 - a. Beta was in excess-in this case only theta was dec.
 - b. Theta was nl but beta dec, then beta was rewarded

Use of qEEG and subtypes-to determine NF protocol

- 2. *Frontocentral alpha* protocol-If there was excess frontocentral alpha (esp during eyes open or EO) then midline site where the activity was greatest was chosen and downtrained. If no excess beta or beta spindles, then beta was rewarded
- 3. *Beta downtraining* protocol-If excess beta or beta spindles (excess high beta can be anxiety) were present then site where they were maximal was selected-and downtrained

Use of qEEG and subtypes-to determine NF protocol

- 4. *Low voltage EEG* –If observed , SMR protocol was used (*If dec alpha power was noted on Eyes Closed (EC), alpha uptraining was done at Pz with EC (Johnston, 2005)*)
- 5. *If no clear qEEG deviations, and/or if sleep problems were a main complaint, SMR was used on side where 12-15Hz activity was lowest.*

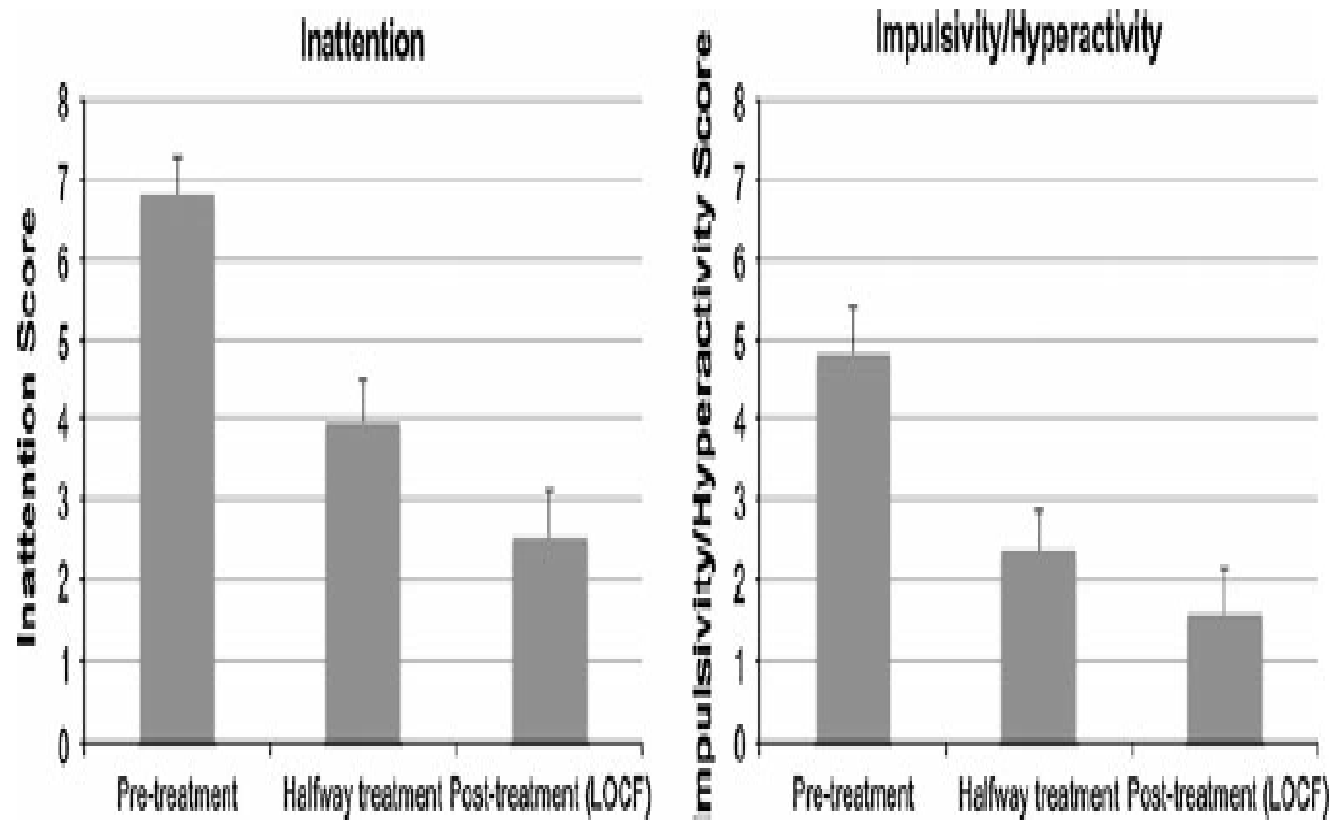
In all protocols, EMG inhibits were employed where EMG (55-100Hz) had to be kept below 5-10 μ V

Use of qEEG and subtypes-to determine NF protocol

Arns, 2009

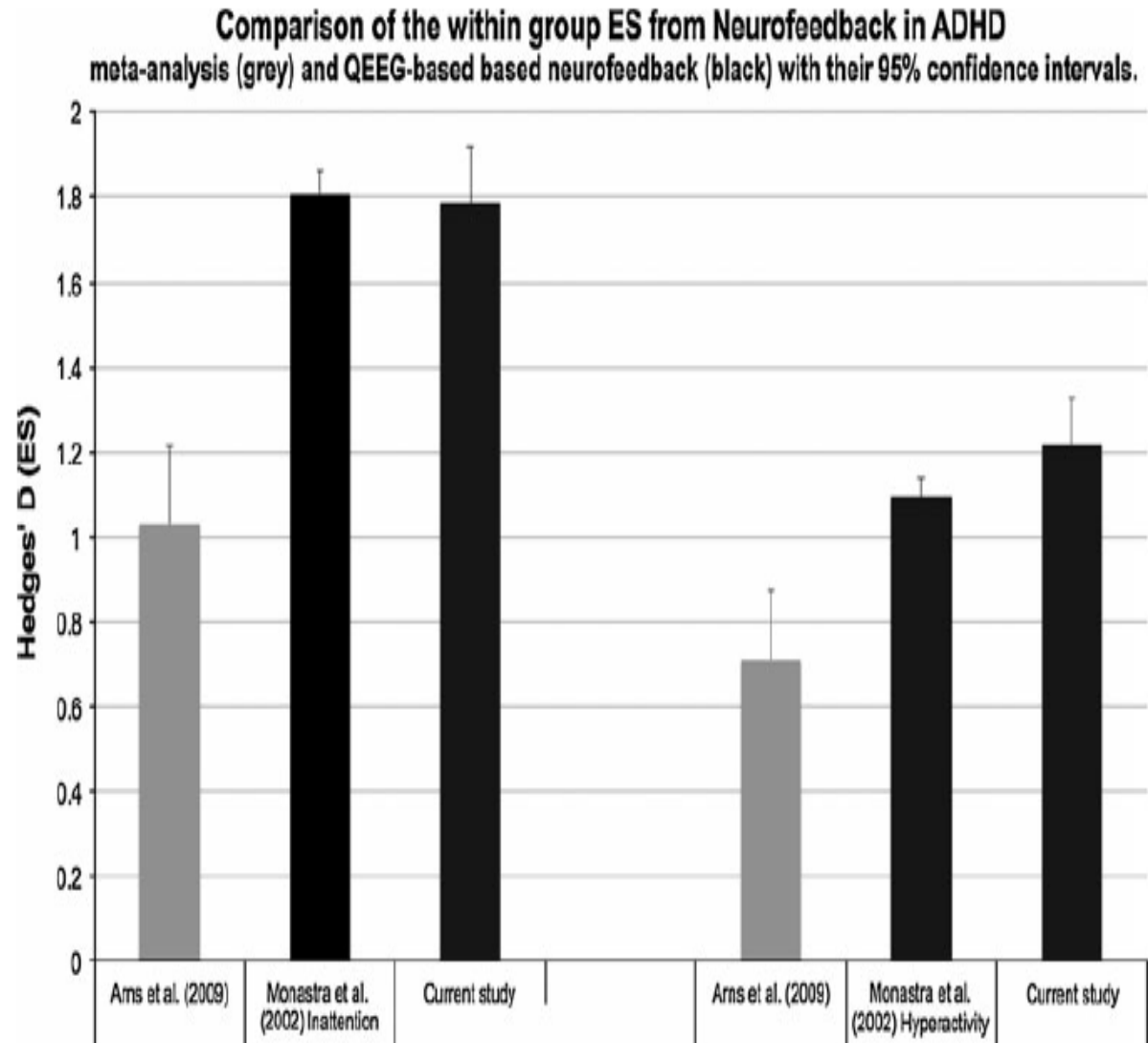
- Results:

Fig. 1 Clinical effects over time for the total group of ADHD/ADD patients at pre-treatment, halfway treatment and post-treatment (averages plus SEM) for ATT and HI. All time effects were significant ($p \leq .001$)



Use of qEEG and subtypes-to determine NF protocol

Fig. 3 ES for the different studies mentioned in the introduction and the ES obtained from the current study, with on the left ES for ATT and on the right ES for hyperactivity. Note that ES for hyperactivity for this study was based on a combined HI scale



Use of qEEG and subtypes

- ES for Attention was 1.78 and for Hyperactivity was 1.22
- Equal to Recent ES reported by Monastra, et al (2002) but double the effect of ES in Arns (2009)
- Recent meta analysis of effects of stimulants medication in ADHD found ES 0.84 for Ritalin for HYP and 1.01 ATT (Faraone and Buitelaar, 2009)

- Other randomized controlled studies
- Choi, et al, 2011, for depression (effect size of 1.06),
- Cortoos, et al, 2010, for insomnia (effect size = 1.04),
- Peniston and Kulkosky, 1991, for Post-Traumatic Stress Disorder (effect size = 1.30)
- Scott, et al, 2005, for alcohol abstinence (effect size = 0.47).
- In meta-analysis (Tan, et al 2009) NF consistently decreased seizures in severe cases of epilepsy which could not otherwise be controlled.

LORETA NF

- Today there are three types of NF that employ the use of qEEG:
- 1. Real time Z score NF (2 channel, 4 channel and 19 channel)
- 2. *Low Resolution Electromagnetic Tomography* (LORETA NF)
- 3. Functional magnetic resonance imaging (fMRI) neurofeedback's

Differences between Surface ZNF and LZNF

- 1. Surface NF involves measuring the amplitude of neurons directly beneath the electrode where 95% of the neurons arise from a distance of 6 cm and all frequencies are mixed together at each electrode.
- However, LORETA uses three-dimensional source localization applied to human qEEG in which the mixture of frequencies under each scalp electrode are unscrambled and linked to three-dimensional sources in the interior of the brain with accuracies of approximately 1 cm in many situations.

Differences between Surface ZNF and LZNF

- 2. Surface ZNF calculates the z-score of identified EEG metrics at various 10-20 surface electrode sites.
- However, with LZNF, the z-score is calculated for a particular collection of current source density (CSD) voxels (4mm-1cm). This makes it possible to conduct NF with the z-scores of the calculated location of deeper cortical dipole generating regions or structures (i.e. cingulate gyrus).
- How was this done?

Low Resolution Electromagnetic Tomography (LORETA)-how was this done?

- In 1994, Robert Marqui-Pascual devised accurate estimates of the deep (lower) brain sources of the EEG patterns in small regional voxels which are (approximately 4 mm 1 cm cubic voxels) coregistered to MRI slices.
- He transformed these raw EEG signals into three-dimensional images that were then coregistered on the Talairach MRI atlas.
- This new method was called LORETA. The Web site to obtain additional information on LORETA is <http://uzh.ch/keyinst/loreta.htm>.

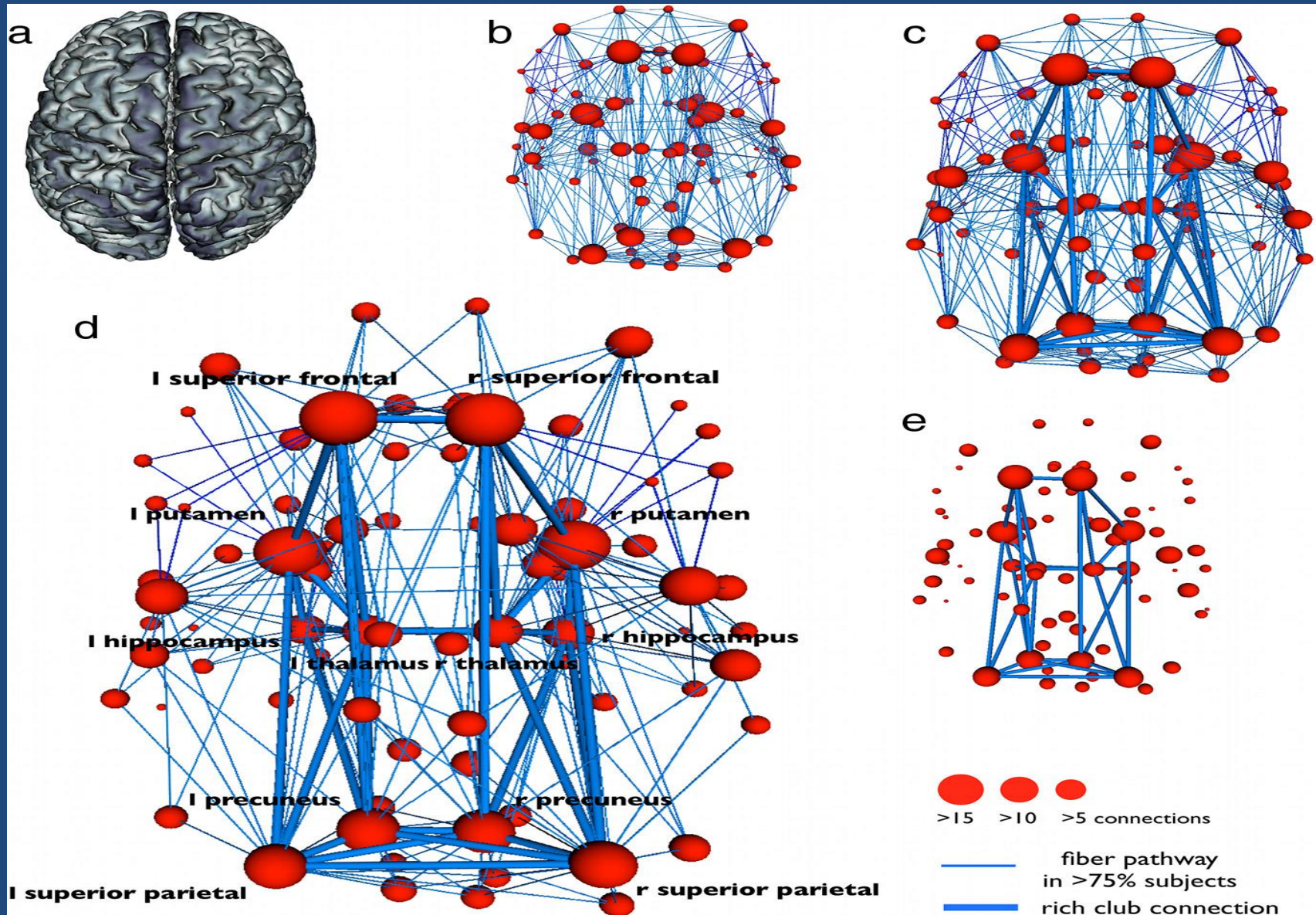
Cross correlation of qEEG with neuroimaging- called Tomography EEG (tEEG)

- qEEG has been co-registered in imaging modalities, including, positron emission tomography (PET), single-photon emission computed tomography (SPECT), fMRI, and DTI and to create a common anatomic atlas.
- The advent of tEEG is important because it provides:
- Therefore, Electromagnetic tomography=changes in the electrical sources in the brain that are associated with changes in blood flow on fMRI.

LORETA NF

- LORETA NF uses a different kind of qEEG NF analysis that provides an estimation of the location of the deep underlying brain generators, called modules or hubs (eg, the anterior cingulate, insula, fusiform gyrus) and networks of the patient's EEG activity within a frequency band.
- Coherence training can include multiple areas.
- The goal is to start with symptoms and then link dysregulation in networks of the brain to the patient's symptoms.

LORETA NF influences “rich club,” characterized by a tendency for high-degree nodes to be more densely connected among themselves than nodes of a lower degree -van den Heuvel & Sporns , 2011



LORETA correlated to fMRI

- In a randomized double blind placebo controlled study using the LORETA phase NF for 30 minutes, there were significant changes in the Default Mode network and the attention network that were verified on fMRI as compared to the sham group ($p < 0.001$)
- (Keeser, 2015)

LORETA NF and ADHD

- 1. Case study using LORETA neurofeedback in a student with ADHD, after only 12 sessions of NFB, his NeuroTrax global cognitive score (<http://www.neurotrax.com/>) rose to 80.1 points overall.
- The patient's memory score increased from 58.1 to 76.7, executive functioning from 49.1 to 74, and attention from 31.6 to 62.7. The family reported improvements with his vocabulary and overall functioning.
- Koberda, 2014

- 2. Case series of 10 children suffering from autism, ADHD, TBI, PTSD, learning disorders, anxiety and depression, each child received medical standard of care.
- Outcome measures included quantitative EEG changes and progress in goal achievement as reported by the child, parents, guardians and teachers.
- Using paired *t*-test comparisons of before and after LORETA data, every subject demonstrated learning with Cohen's *d* ES for CSD in the region of interest (ROI) from small to large effect sizes (ES) ranging from 0.5 to 4.6 with an average of 1.4.
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- Koberda, et al, 2014

- 3. Case study
- Delayed speech
- ADHD dx.
- Could not write or read
- Low iron/vitamin D and zinc
- Food sensitivities
- Dysbiosis due to antibiotics for recurrent ear infections

- LORETA NF

- | | PRE | POST |
|---------------|---------------------------|--------|
| Word ID | 1.1 grade equivalent (GE) | 1.8 GE |
| Word attack | 1.7 GE | 3.2 GE |
| Word | | |
| Comprehension | 1.2 GE | 2.4 GE |
| Passage | | |
| Comprehension | 1.0 GE | 2.1 GE |
| TOVA | 3.7 | 1.6 |

Summary LORETA NF

- Even 30 seconds of LORETA NF has shown changes in the DMN and the attention networks on fMRI
- Although only case studies have been reported using LORETA NF for ADHD, the fewer sessions required and promising ES statistics shows promise.
- LORETA allows monitoring of NF changes because:
 - 1. LORETA unscrambles frequencies and locates source in voxels deep within the brain
 - 2. Location of voxels deep within the brain are co-registered with MRI and can be seen in 3 dimensional correlations
 - 3. Co-registration of qEEG with neuroimaging is called tEEG=changes in the electrical sources in the brain that are associated with changes in blood flow on fMRI
 - 4. LORETA NF influences the rich club nodes where more connections are seen in the brain and this influences coherence (de Ridder, 2015)
- Studies are small
- More research is needed.

Enduring effects

- 1. Steiner, et al, 2011 F/U at 6 months --- demonstrated that NF students maintained the same medication dosage but
- Students getting cognitive training and control groups had statisically significantly increases in meds (9 mg, $p=.002$ and 13 mg, $p<.001$)
- 2. At 6 months to 2 years (Gani, et al, 2008, Gevensleben, et al, 2010, Leins, et al, 2007, Strehl, et al, 2006) demonstrated that NFeffects did not fade over time and impulsivity and hyperactivity effects continued to improve.
- See next graphs-bar to right is controls

F/U studies, Gevensleben, 2010-inattention=L, hyperactivity=R

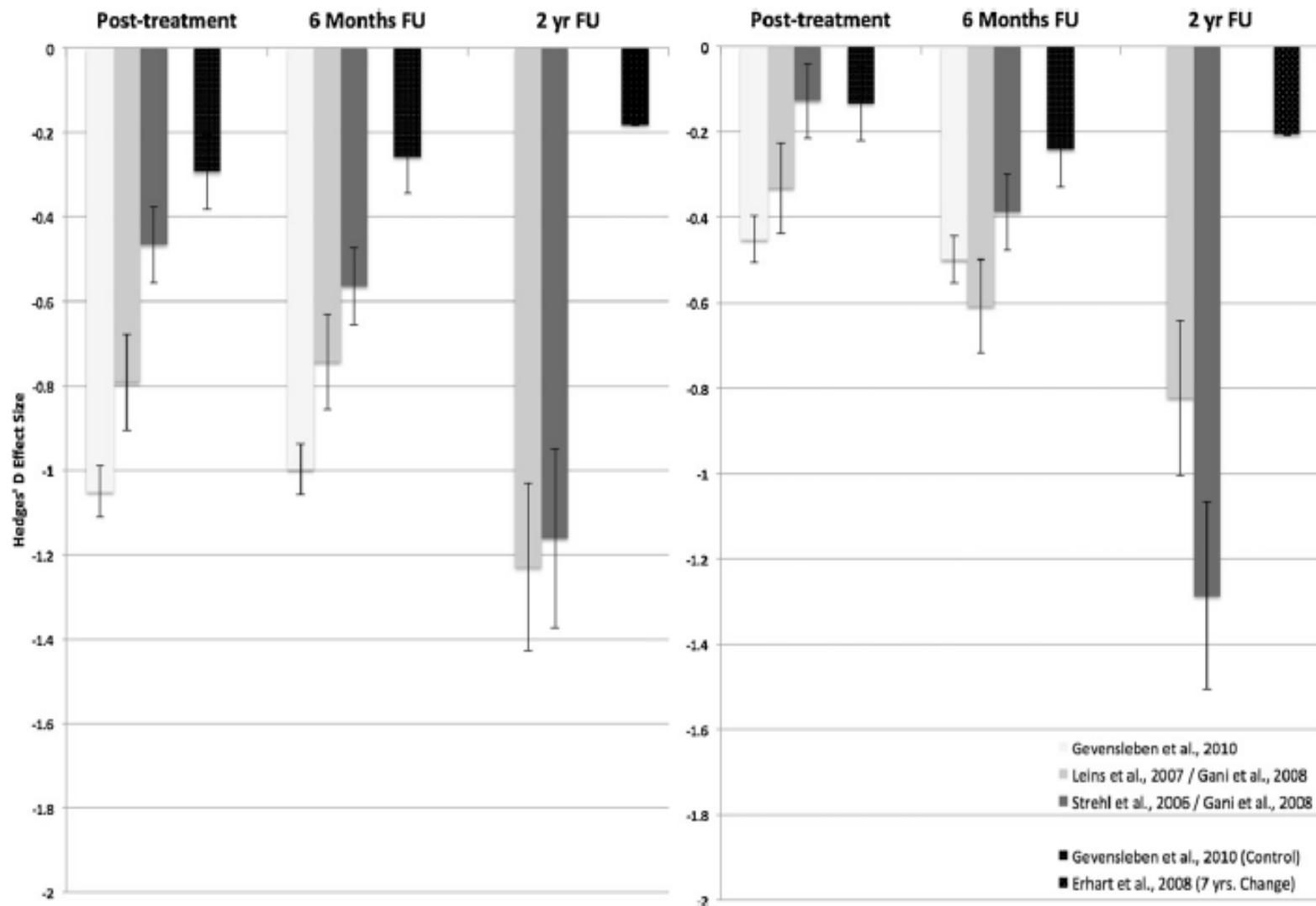


Fig. 2. Within subject Hedges' D ES for 3 randomized studies who have performed 6 month and 2 year follow-up data for inattention (left) and hyperactivity (right). For Post-Treatment and 6 month follow-up the ES for the control group from the Gevensleben et al., (2010) study has been plotted as a comparison for non-specific effects across time. For the comparison at 2 years follow-up the ES of 7- 10 yr. vs. 14- 17 yr. children has been plotted as an indication of improvements of ADHD symptoms related to aging from Erhart et al. (2008). Note that for all studies the effects of neurofeedback tend to increase with time, most specifically for hyperactivity. (Error bars are Variability of the ES.)

Long Term Effects-Arns et al,2012

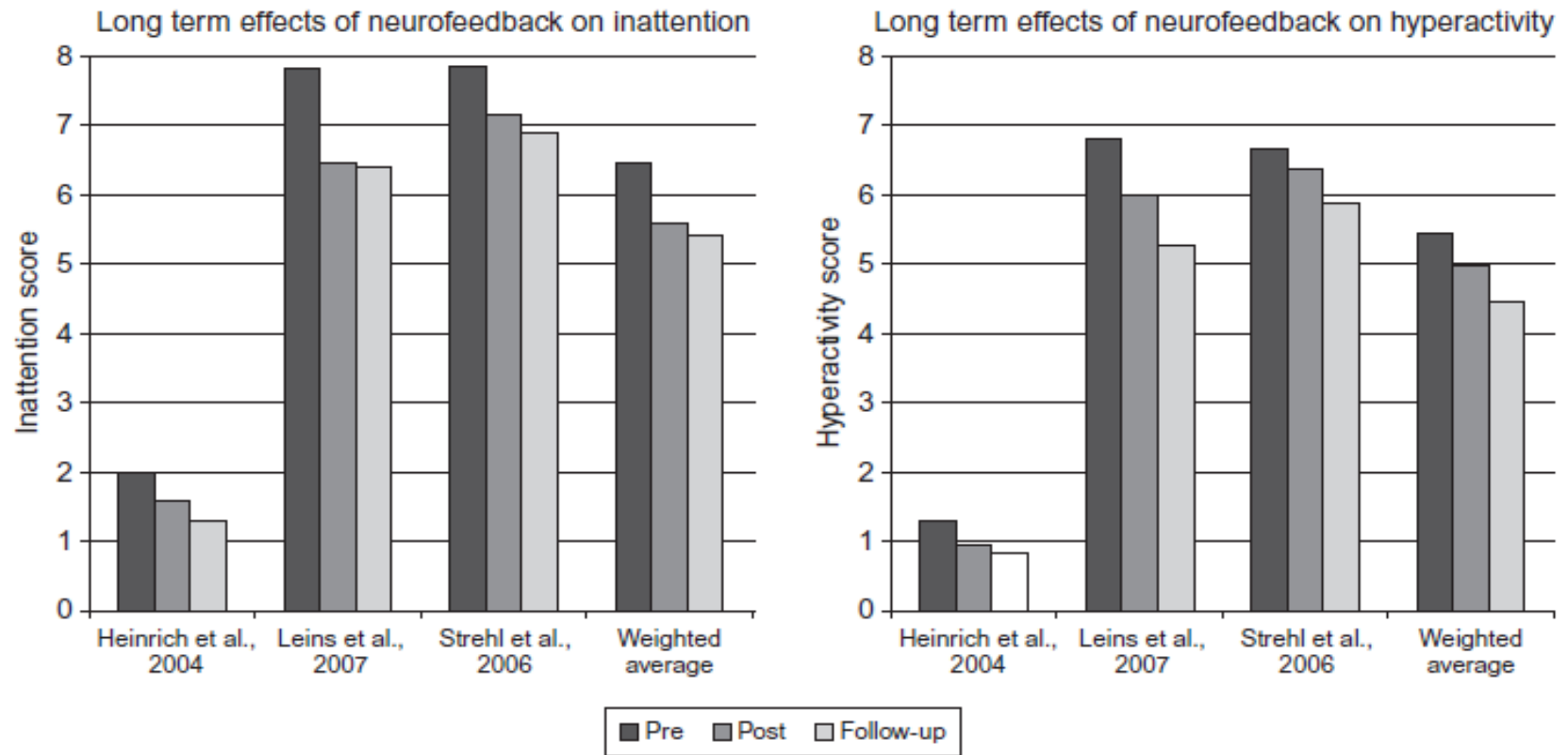


Figure 15.1 The effects of neurofeedback over time for three controlled studies for inattention (left) and hyperactivity (right). The study by Heinrich et al. performed 3 months follow-up and the other two studies performed 6 months follow-up. Note that the effects of neurofeedback tend to improve further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

- 3. The enduring effects of neurofeedback in children with ADHD and learning disorders
- EEG maturation correlated to Theta/Beta ratio, WICS scores and TOVA scores
- **After two years, the EEG maturational lag in the Control Group:**
 1. High theta/beta ratios continued to increase in temporal and frontal areas
 2. The absence of positive behavioral changes, observed initially after the study, continued and the neurological diagnosis remained LD.
- **In contrast, after 2 years the EEG maturation in children who belonged to the Experimental Group with previous NF training.:**
 1. Positive behavioral changes continued to improve, which were reflected in remission of LD symptoms (TOVA and Performance IQ significantly improved)
 2. Theta/beta ratio sustained improvement.
- This study lends credibility to the idea that ADHD may be due in part to a developmental delay but this is a small study and more research is needed.
- Becerra, et al, 2006

- 4. Monastra, et al,2009 study all subjects in the experimental and control groups were on medication.
- When the medication was removed at the end of treatment only the participants who had completed NF were able to sustain their improvements.

Summary

In summary, preliminary results of surface NF has shown a greater effect size than medication when a qEEG analysis is used to detect which patients will be more likely to respond.

In addition, unlike medication, these early studies of surface NF demonstrate lasting effects when the intervention is discontinued and the effects continue to endure, especially in regards to hyperactivity as opposed to students who stay on medication.

Also important is the fact that when students remain on medication, those who do NF seem to require less increases in medication as compared to controls or students who receive cognitive training.

EEG Maturational lags in theta (associated with ADHD and LD) continued to worsen in controls but in the NF group maturational lags in theta continued to improve and, in some cases normalize 2 years after NF.

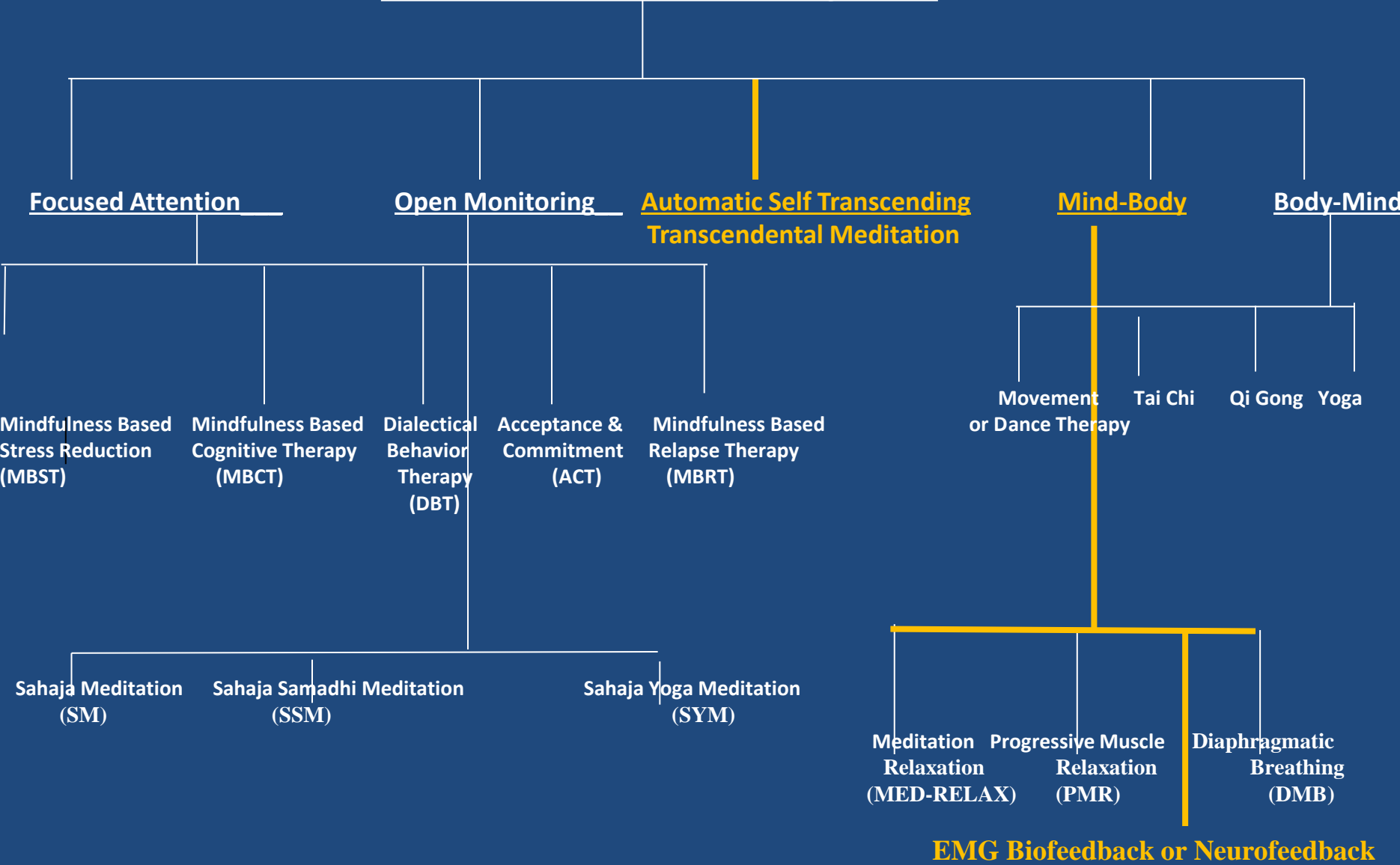
Studies were small except for the Monastra study. More research is needed

CIM in ADHD

- All of the following studies need replication or more research
- However, if you use some of these interventions in your office, it is recommended that you use the following guidelines (Arnold, 2013):
 - Safe
 - Easy
 - Cheap
 - Sensible
- Examples of these interventions include a protein-containing low-sugar breakfast, omega-3 fatty acids, RDA/RDI multivitamin/mineral supplementation (especially in deficiencies) minimization of food dye ingestion, reasonable refined sugar restriction, elimination diets, neurofeedback, meditation and probiotics

Simkin, 2014

Meditation studied in youth



Meditation-

- 5 categories of meditation
- A. Attention training-refers to the activity of intentionally paying attention, to a particular object for a particular purpose.
- B. Open Monitoring-includes all forms of meditation practice, which emphasize awareness or "mindfulness"-awareness of thoughts and feelings moment to moment in a non-judgmental way.
- C. Transcendental Meditation or Automatic Self Monitoring
- D. Mind Body-combination FA and/or OM sometimes with relaxation techniques
- E. Body Mind-combination of FA, OM and sometimes TM with movement added

- A. 5 types of attention or concentration training training:
- Mindfulness Based Stress Reduction (MBSR) (Kabat-Zinn, 2003, 2012)
- Mindfulness Cognitive Behavior Therapy (MBCT)(Segal et al, 2002)
- Dialectical Behavior Therapy (DBT) —(Linehan, 1993)
- Acceptance and Commitment Therapy (ACT) (Hayes, 2004)
- Mindfulness Based Relapse Therapy (MBRT) (Witkiewitz, 2010)

- B. 3 types Open Monitoring:
- Sahaja Meditation (SM),
- Sahaja Samadhi Meditation (SSM) and
- Sahaja Yoga Meditation (SYM) (Harrison, et al, 2004-study done in children)

- C. Transcendental Meditation (Automatic Self Transcending or AST)
- D. Mind-Body:
 - 1. Relaxation techniques, including Meditation-Relaxation (MED-RELAX) , (Catani, et al, 2009)
 - 2. Progressive Muscle Relaxation (PMR),
 - 3. Other Relaxation (OR) including Electromyographic (EMG) biofeedback (AR) as described by Eppley or EEG biofeedback (neurofeedback) alone or with relaxation techniques.
 - 4. Deep breathing Meditation (DBM) is the M-B used with test anxiety (Paul, 2007)
 - 5. A method described by Fisher (2006) as : Posture, Breathing, Attention and Visualization

- E. Body-Mind
- Most frequently mentioned in child and adolescent research:
 - 1. Yoga —(Carei et al, 2010, Noggle et al, 2012)
 - 2. Tai Chi-(Hernandez-Reif et al, 2001, Wall, 2005)
 - 3. Qi Gong —none done with youth
 - 4. Exercise (Doop et al 2012)
 - 5. Movement or Dance Therapy (Hartshorn et al, 2001, Rosenblatt et al, 2011)

Mindfull studies on ADHD

- Non-randomized studies using a combination of MBST/MBCT has been used for ADHD in children with parallel training for the parents.
- In one study (VanderOord, et al, 2012) although there was only a slight improvement in attention, family harmony did improve.
- However, in another study, (Zylowski, 2008) neurocognitive tests did seem to show an improvement in inhibition and self-regulation.

- A randomized study using MBST/MBCT demonstrated is improvement in visual attention and test anxiety but not sustained attention (Napoli, et al, 2005).
-
- A study using MBCT found that using the technique helped to reduce anxiety, thereby increasing attention and affective self-regulation.
- Therefore, MCBT was indirectly responsible for increasing attention (Semple, et al, 2010).
-
- The use of Mindfulness techniques clearly demonstrated better outcomes when participants adhered to the recommended meditation frequency and duration (Biegel, et al 2009)

- TM
- A small study did show a corresponding decrease in problematic symptoms associated with working memory, planning, organization, ability to inhibit and shift, and expressive attention (often seen in ADHD) when anxiety and depression symptoms decreased.
- Although the study lacked randomization and blinding, it is important because it demonstrated improvement in ADHD symptoms and executive function across several comorbid conditions.
- Caution should be used in interpreting self-reports by adolescents (used in this study) but the neurocognitive testing gives stronger evidence about the effect of TM on cognitive functions.
- (Grosswald, et al 2010)

TM

- In a randomized pilot study using TM for three months resulted in significant decreases in theta/beta ratios (seen in some children with ADHD-see neurofeedback section) and improvements in coherence (connections between areas in the brain).
- These brain measures were supported by significant increases in Letter Fluency and significant increases in positive behavior reported by the parents (Travis, et al, 2011).
-
- Three double blind placebo controlled studies (n=362) using TM increased attention and cognitive abilities in youth in a school setting who were not identified with ADHD (So, et al, 2001)

- Mind-Body
- No studies for ADHD have been done using Mind-Body techniques except NF
-

Body -Mind

- A small study in 13 adolescents using Tai Chi was significant for less anxiety, less daydreaming, fewer inappropriate emotions, and less hyperactivity.
- Limitations to the study were no control groups, no randomization, and small sample size (Hernandez-Reif, et al, 2001).
-
- The effects of exercise have been studied in youth with ADHD.
- The main cumulative evidence indicates that short-term aerobic exercise, based on several aerobic intervention formats, seems to be effective for mitigating symptoms such as attention, hyperactivity, impulsivity, anxiety, executive function and social disorders in children with ADHD (Cerilloo-Urbina, et al,2015).

- In a small randomized controlled yoga study, all outcome measures (test scores on an attention task, and parent ratings of ADHD symptoms) the yoga training was superior to a group doing motor training, with effect sizes in the medium-to-high range (0.60-0.97).
- All children showed sizable reductions in symptoms over time (Heffner, et al 2006).
- In another study, significant improvements from pre-test to post-test were found for the yoga, but not for the control group on five subscales of the Conner's' Parents Rating Scales (CPRS): Oppositional, Global Index Emotional Lability, Global Index Total, Global Index Restless/Impulsive and ADHD Index.
- However, significant improvements were not seen on three CPRS subscales: Hyperactivity, Anxious/Shy, and Social Problems (Jensen, et al, 2004).

Nutrition

- 1. Artificial food colorings
- One study selected 200 participants of hyperactive children, and found that:
 - 150 improved with elimination of artificial food coloring (food dyes), and deteriorated when food coloring was re-introduced.
 - Thirty four of these reactors and 20 controls entered a double-blind challenge with six doses of tartrazine (FD&C Yellow 5) and placebo.
 - Of these, 22 of the 34 reactors (65%) and 2 of the 20 controls (10%) clearly reacted to the dye challenge with irritability, restlessness, and sleep disturbance (Rowe and Rowe, 1994).
-
- The first double blind placebo controlled study to look at the effect of additives and ADHD was in Britain and involved 1,873 three year old children.
- It involved benzoate and ARC's.
- The findings suggested that significant changes in behavior could be produced by the removal of artificial colorings and sodium benzoate (David, et al , 1987).

- Genetics and AFC's
- Three genes have been found to moderate the effect of AFC's on hyperactivity.
- Two of these genes involved histamine
- One is HNMT Thr105I1e and the other is HNMT T939C.
- A third is the dopamine gene DAT1.
- The C allele of one gene (HNMT T939C) was found to be protective against the effects of AFC's (Carter, et al, 1993, Egger et al, 1985, Rowe and Rowe, 1994).

- AFC's and zinc
- Studies suggest zinc wasting (excessive excretion) from tartrazine and sunset yellow, may be associated with the behavioral changes.
- These AFC's may bind or chelate zinc whereby it is then excreted through the kidneys.
- In studies where these AFC's was added to the diet of children who had ADHD and whose ADHD symptoms got worse, Zinc levels decreased (Arnold, et al, 2012, Ward, et al, 1990, Ward, 1997)

- 2. Food sensitivities
- In one study, the diet consisted of the few foods diet (ie, rice, meat, vegetables, pears, and water) complemented with specific foods such as potatoes, fruits, and wheat.
- If after 2 weeks, no changes occurred, other foods were eliminated.
- Of 78 children diagnosed with ADHD who tried the diet, 59 of them improved.
- However, when re-exposure to the foods occurred, 47 children relapsed after the challenge (60%).
- There was no correlation to food sensitivity lab results.(Pelser, et al,2001).

- |
 - What are indicators of food sensitivities?
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 - Allergic shiners
 - History of colic
 - History of eczema
 - History of reflux
 - Long bone pain
 - Belly pain, Irritable Bowel syndrome
 -
 - Family history of atopy (asthma, hives, hay fever)
 -
 - (Schmitt, et al, 2013)
 -
 - However, all of the indications listed under the Feingold diet may be indicated, as well.
- | | |
|--|-------------------|
| | Foot odor |
| | History of otitis |
| | Runny nose |
| | Insomnia |
| | Constipation |
| | Bad breath |

- 3. Probiotics
- In a recently published study, seventy-five infants who were randomized to receive *Lactobacillus rhamnosus* or placebo during the first 6 months of life were followed-up for 13 years.
- Gut microbiota was assessed at the age of 3 weeks, 3, 6, 12, 18, 24 months, and 13 years of age.
- At the age of 13 years old, ADHD or AS was diagnosed in 6/35 (17.1%) children in the placebo and none in the probiotic group ($P = 0.008$).

- The mean (SD) numbers of *Bifidobacterium* species bacteria in feces during the first 6 months of life was lower in affected children 8.26 (1.24) log cells/g than in healthy children 9.12 (0.64) log cells/g; $P = 0.03$.
- Although this study does not definitively associate the use of probiotics with a decreased risk for developing ADHD and autism, probiotic supplementation early in life may reduce the risk of neuropsychiatric disorder development later in childhood possible by mechanisms not limited to gut microbiota composition. (Partty, et al, 2015)
- In another study individuals were given probiotics for 30 days. Those on the probiotics had less psychological stress than the control group (Serino, et al, 2013)

- Microbes more likely exert a bottom up effect
- However, stress can influence microbes and their gene expression , as well.
- Microbes outnumber cells in the body by 10:1 and this means there are >150 times the number of genes in microbes than there are in the human body
- There are 1000 bacterial species and > than 7,000 strains (Collins et al, 2012)

- Another more comprehensive diet is being used at Cleveland Clinic in regards to Functional Medicine. It has the following components:

-

- Foods to Remove

-

- Dairy

- Eggs

- Gluten grains

- (barley, rye, spelt, wheat)

- White (table) sugar

- Shellfish

- Soy

- Beef

- Pork

- Processed meats

- Peanuts

- Caffeine and

- Chocolate

-

Foods to eat:

Chicken, fish and turkey

Extra virgin olive or coconut oil

Unsweetened Cashew,
coconut & almond milk

Clarified butter

Vegetables

Fruits

Rice, potatoes and sweet
potatoes

All nuts except peanuts

Legumes

Seeds

Non- gluten grains

Role of sugar

- The recommended amount of sugar a person should eat per day by the American Heart Association is 5-8 grams.
- However, most Americans eat about 41 grams per day.
- Eating too much sugar, artificial sweeteners can cause an imbalance in the normal bacteria to yeast ratio (80%/20%) in the gut.
- Yeast live off of sugars and artificial sweeteners.
- When the intake of sugars and artificial sweeteners increases yeast may begin to overgrow in the gut.

- The toxins produced by these yeast may enter the bloodstream in individuals with leaky gut.
- This process causes inflammation and symptoms, such as, brain fog (due to poor circulation), acne, fatigue, bloating, constipation, diarrhea, nail fungus and yeast infections.
- Reducing yeast in the gut can be done by taking probiotics.
- In a recent study a twelve-month administration of a combination preparation with 8 bacterial strains to 10 patients—in comparison to placebo therapy—gave the desired maintenance of remission and also significantly reduced the diversity of intestinal fungi (Kühbacher, et al, 2006).

Organic foods

- A study of 1,139 youth with ADHD found that 94% had high levels of organophosphate pesticides.
- Those youth with higher levels had a 10 fold increase in the risk of ADHD (Bouchard, et al, 2010).
- Higher levels can also be found in individuals who are slow or intermediate metabolizers of the liver enzyme 2D6 enzyme that breaks down pesticides
- In fact, genetically slow CYP2D6 metabolizers are at higher risk for developing Parkinson's disease, a risk that increases with exposure to pesticides.
- High levels of pesticides can deplete glutathione.

- N-acetylcysteine (NAC), best known for its ability to counter acetaminophen (Tylenol) toxicity, is a safe, well-tolerated antidote for cysteine/GSH deficiency (Atkuri , et al, 2007).
- Glutathione (GSH) deficiency is associated with numerous pathological conditions. Administration of NAC, a cysteine prodrug, replenishes intracellular GSH levels.
- Although the effect of NAC has been studied in addiction, compulsive and grooming disorders, schizophrenia, autism and bipolar disorder, with promising results, the effect of using NAC in ADHD in youth has not been studied, especially in those individuals identified as having higher levels of pesticides or who are slow metabolizers of 2D6

Omega 3 fatty acids

- Omega 3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce inflammatory makers like C-reactive protein, interleukin 6 , and TNF alpha (Li, et al, 2014).
- Omega 3 fatty acids that are higher in eicosapentaenoic acid (EPA) than docosahexaenoic acid (DHA) seem to help with attention in children with ADHD, although the effect was modest (Bloch, et al, 2011).
- However, another study demonstrated that Omega 3 fatty acids which were bound to phosphatidylserine (PS) revealed a significant reduction in the ADHD-Index and hyperactive components.
- Data from the open-label extension indicated sustained efficacy for children who continued to receive PS-Omega3 (Manor, et al 2012)

- Omega three fatty acids can cause mercury contamination and only mercury free forms should be used .
- Also, omega 3 fatty acids can cause bleeding and should be stopped 2 weeks prior to surgery.
-
- Common side effects:
-
- Dyspepsia, nausea, diarrhea, increased bleeding
-
- Uncommon side effects:
-
- Gastrointestinal symptoms, upper abdominal pain, allergic hypersensitivity, dizziness, headache, increased low-density lipoprotein (LDL) or alanine aminotransferase (ALT) levels, mania, depression
-
- Rare side effects:
-
- Hyperglycemia, headache, gastrointestinal pain, hepatotoxicity, acne, pruritic rash, ventricular tachycardia
-
- Very rare side effects:
-
- Hypotension, urticaria, nasal dryness, gastrointestinal hemorrhage, hemorrhagic stroke, increased blood lactate dehydrogenase (LDH), hemolytic anemia
- (Arnold, et al, 2013)

Zinc deficiency

- Zinc is an important cofactor for metabolism relevant to neurotransmitters, prostaglandins, and melatonin, and indirectly affects dopamine metabolism.
- The use of zinc reduced the optimal dose of stimulant by over a third.
- However, the most effective dose was 30 mg of chelated zinc per day (Akhondzadeh, et al, 2004).
- Although the results are promising, more research is needed.

Iron deficiency

- Iron is used to synthesize the neurotransmitters dopamine and norepinephrine.
- Ferritin is a measure of iron stored in the body.
- The optimal level for children with ADHD is between 40-60 ng/ml (Konofal, et al, 2007, Oner, et al 2008).
- One study demonstrated that when ferritin levels were low, amphetamines used in the treatment of ADHD were less effective (Calarge, et al 2010).
- Two small studies have shown a decrease in ADHD symptoms in youth with low iron levels when supplemented (Oner, et al, 2008, Sever, et al, 1997).
- Iron supplementation should only be used when a deficiency is seen and at doses between 7-15mg/d .
- Risk Factors
- Levels of iron levels should be checked because excess iron can cause hemochromatosis (where iron is deposited in organs). Iron can also cause constipation.

Broad Spectrum Micronutrients

- Broad spectrum micronutrients are required for many critical biochemical reactions to occur, ranging from manufacturing neurotransmitters, to providing the mitochondria with essential nutrients for energy production, to assisting the gut to heal from inflammation
- In a trial study by Walsh, et al, (2004) 207 youth with ADD, conduct disorder or oppositional defiant -disorder were given broad spectrum micronutrients (micronutrients, amino acids, etc.).
- There was a 92% decrease in physical assaults.
- In this study 58% did not display anymore physical assaults .
-

- Broad Spectrum micronutrients
- In double blind placebo controlled study using micronutrients, by Schoenthaler and Bier, children (age 6-12 years old) in a public school with conduct disorder were given a vitamin-mineral formula at 50% of RDA levels for 4 months.
- In the group that received the vitamin-mineral formula, there was a 47% reduction in violent and non-violent misconduct (Schoenthaler, et al 2000).
- These products should never be used without supervision-especially in patients on psychotropics due to risk of worsening conditions.-mania

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- Magnesium deficiency
- A study that was done on children with ADHD and low magnesium levels demonstrated a significant effect ($ES=1.2-1.4$) in those youth treated with 200 mg of magnesium per day after 6 months.
- Magnesium glycinate has been used by clinicians at 200-400mg/d. No studies have shown magnesium to be beneficial in children with ADHD and normal levels of magnesium (Starobrat-Hermelin, et al, 1997, Arnold et al, 2013).
-
- Risk factors
-
- Magnesium supplementation can be toxic and should not be given above 10mg/kg/day.
- Therefore, caution should be used when supplying with magnesium in youth without a deficiency.

- Broad spectrum micronutrients are available on the market in many products with different ingredients and different dosages. Caution should be used in using any of these products without physician supervision. **They are not without risk.**
-
- Mild side effects include: diarrhea, nausea, insomnia, headache and flatulence. Anxiety can occur if dosages are too high.
-
- These products do have drug-drug interactions and when taking antibiotics the nutrients may not be absorbed.
-
- Strict contraindications include patients with a history of Wilson's disease, Hemochromatosis and hemosiderosis, Phenylketonuria, and Trimethylaminuria.
-
- Extreme caution should be used with patients with a history of drug dependence (illicit drugs, caffeine, alcohol and nicotine), medications which can cause withdrawal syndromes, other drugs with central nervous system effects, treatment resistant Candida, autoimmune thyroid disease (Hashimoto's) and goiter, hyperlipidemia and severe protein malnutrition. The latter may cause vitamin A toxicity .
- (Popper, 2014)

- L-carnitine
- Two randomized controlled studies showed a weak effect on inattention in youth with ADHD.
- L-carnitine is used to carry fatty acids into mitochondria for energy and may help indirectly with inattention, in this way.
- It may make hyperactivity and impulsivity worse. The maximum effects take about 4 months (Arnold, et al 2013, Arnold, et al ,2007).
- More research is needed.

Sleep

- Melatonin is a hormone that has been studied in two clinical trials and one randomized controlled study for the treatment of ADHD found an improvement in sleep onset but no improvement in ADHD.
- (Tjon Pian , et al 2003, van der Heijden, et al, 2007, Weiss, et al, 2006)
- Risk factors
-
- Melatonin may worsen seizures in youth with epilepsy and may cause bleeding when used with blood thinners like warfarin (Arnold, et al, 2013).

- Obstructive sleep apnea
- In full syndromal ADHD, a high incidence (20% to 30%) of obstructive sleep apnea (OSA) has been shown .
- In a review of 6 interventional studies, improvements in behavior, inattention, and overall ADHD after treatment of OSA occurred (Youssef , et al, 2011).
- Children with a history of snoring and ADHD should have a sleep study.
- In a prospective study following 114 children who had a tonsillectomy for OSA, 28% had symptoms of ADHD.
- One year later, 50 %of those that had ADHD no longer meet criteria for the disorder (Suratt, et al, 2006)

Herbs

- Pycnogenol-how does it work?
- Role in oxidative stress.
-
- Damage to DNA can be caused by the out of control production of oxygen free radicals inside cells
- Antioxidants can counter the over production of oxygen free radicals by scavenging these free radicals.
- Pycnogenol is a powerful anti-oxidant.
- ADHD is thought to be due to an imbalance of neurotransmitters like dopamine.
- This imbalance may lead to oxidative stress and the overproduction of oxygen free radicals, which may destroy neurons.
-

- In a double blind placebo controlled study of 61 children, children with ADHD and controls were measured for the level of 8-oxoG, a marker of oxidative damage to DNA.
- Children with ADHD had significantly higher levels of 8-oxoG than children without ADHD.
- The use of pycnogenol at 1 mg/kg per day not only decreased the level of 8-oxoG but had a significant effect on the ADHD symptoms.
- When pycnogenol was stopped, the effects were lost (Trebatická, et al 2006, Chovanová, et al 2006).
-

- 2. Role with glutathione, GSH and GSSH
-
- Pycnogenol increases the production of glutathione, another powerful antioxidant. GSH (γ -glutamyl-cysteinyl-glycine) plays a key role in the protection of proteins, lipids and nucleic acids against free radical damage.
- Pycnogenol, by scavenging free radicals, spares GSH (a reduced form of glutathione that is also a powerful antioxidant) by preventing it from being oxidized to GSSH (which causes a loss of antioxidant capacity).

- In a double blind placebo controlled study, 43 children with ADHD were randomized to receive 1mg/kg per day of pycnogenol or placebo
- The children who had received pycnogenol had a 22% decrease in GSSH. GSH/GSSG ratio in patients with ADHD at the beginning of the trial as 35.93.
- After Pycnogenol treatment, the GSH/GSSG ratio rose to 52.26 ($P = 0.05$). After a wash-out period, the ratio decreased again to 42.45. In a placebo group, the ratio GSH/GSSG was unchanged (Dvoráková , et al, 2006).
- More research is needed to determine if this change in the GSH/GSSH ration can decrease the symnptoms of ADHD to significant levels.

- 3. Role of pycnogenol and zinc and copper levels.
-
- Copper has long been known to increase oxidative stress which leads to free radical formation.
- Zinc tends to reduce oxidative stress.
- Pycnogenol contains polyphenols which act as antioxidant but they can also bind to metals ions like copper and iron.
- Zinc and iron are associated with dopamine metabolism.
- Based on the above information, ideally one would want normal levels of iron and zinc and low levels of copper.

- A study found lower zinc levels and higher copper to zinc levels in children with ADHD as compared to controls.
- No differences between selenium and lead levels were found in the two groups.
- The lower zinc levels were associated with parent and teacher scores for inattention and the higher copper/zinc ratios were associated with teacher scores for inattention (Viktorinova, et al, 2015)

- A study by the same above author found that pycnogenol decreases copper levels and copper/zinc levels.
- However, the article was withdrawn from pub med.
- There is no other study correlating the use of pycnogenol and a reduction in ADHD symptoms as well as lowering copper and copper/zinc ratios. More research is needed.
- 4. Pycnogenol can increase nitric oxide which can relax blood vessels and increase blood flow to areas. However, this effect has never been correlated to improved symptoms of ADHD in youth taking pycnogenol.

- Ginkgo biloba
- There was a study comparing ginkgo biloba to methylphenidate for six weeks in youth. Methylphenidate did show a significant improvement in ADHD symptoms but ginkgo biloba did not show improvements (Salehi, et al 2010).
- Due to the risk for subdural and anterior eye bleeds as well as many drug-drug interactions (monoamine oxidase inhibitors, alprazolam, haloperidol, warfarin, and nifedipine), it is not recommended for the treatment of ADHD (Diamond, et al, 2012, Salehi, et al, 2010).

- St John's Wort
- St John's Wort works much like an antidepressant by targeting the neurotransmitters serotonin, norepinephrine, and dopamine.
- In one study unmedicated children with ADHD were given 300 mg or placebo.
- No significant difference was observed by parents (Weber, et al 2008).
-
- Risk factors associated with the use of St. John's Wort include solar sensitivity and serotonin syndrome.
- The latter can cause seizures.
- Therefore it is not recommended for children with ADHD

- Bacopa
- A meta-analysis of Bacopa monnieri (an ayurveda medication used in India) in 437 eligible subjects showed improved cognition on neuropsychological testing and decreased choice reaction time (Kongkeaw, et al, 2014).
-
- The use of Bacopa at a dose of 225 mg/day for a period of 6 months was studied in an open label trial with children with ADHD.
- The specific formulation used in the study was BacoMind (M/s Natural Remedies, Bangalore, India).
- Bacopa significantly reduced the subtests scores of ADHD symptoms, except for social problems.
- The symptom scores for restlessness were reduced in 93% of children, whereas improvement in self-control was observed in 89% of the children.

- The attention-deficit symptoms were reduced in 85% of children.
- Similarly, symptom scores for learning problems, impulsivity, and psychiatric problems were reduced for 78%, 67%, and 52% of children, respectively.
- It was observed that 74% of the children exhibited up to a 20% reduction, while 26% of children showed between a 21% and a 50% reduction in the total subtests scores (Dave, et al, 2014).
-
- Risk factors
- Many of these preparations are not inspected by the Federal Drug Administration and may have infiltrates. Caution is advised when using these compounds. More research is needed to determine if these products will be helpful and standardization and determination of safety of the products should be done.

Chinese herbal medicine

- A compounded herbal product called Nature and Clarity was used in a randomized controlled study of children with ADHD (1).
- The product contains :
- *Paeoniae Alba* (which has been shown to increase noradrenaline-releasing action and enhancement of cerebral oxygenation
- *Withania Somnifera* enhances acetylcholine receptor capacity known to help with memory ,
- *Centella Asiatica* (Gotu kola) demonstrated increased neurite elongation, dendritic growth (5), and improved learning and memory
- High in B-vitamins and is thought to be a cofactor in the synthesis and functioning of serotonin, norepinephrine, dopamine, acetylcholine, as well as GABA , *Spirulina Platensis* supplies essential fatty acids, B vitamins, folic acid, vitamin C, vitamin D, and vitamin E, as well as potassium, calcium, chromium, copper, iron, magnesium, manganese, phosphorus, selenium, and zinc, and all essential amino acids
- *Bacopa Monieri*, and Lemon balm which is used for sleep (*Mellissa Officinalis*)

- Children were randomly assigned to the herbal treatment group ($n = 80$) or control group (placebo; $n = 40$). Seventy three patients in the treatment group (91%) and 19 in the control group (48%) completed the 4-month trial.
- Outcome measure: Test of Variables of Attention (TOVA) administered before and after the treatment period; overall score and 4 subscales.
- The treatment group showed substantial, statistically significant improvement in the 4 subscales and overall TOVA scores, compared with no improvement in the control group (Katz, 2010).
- Chinese herbal medication may have many infiltrates and have to be used with caution.

- Ginseng
- Red ginseng may regulate adrenal function by suppressing catecholamine secretion and cortisol
- Given that imbalances in adrenal corticosteroids such as cortisol and DHEA may contribute to the mood and attention disorders of adolescents with ADHD (Ko, et al, 2014, Goodyer, et al. 2000)), it is possible that treatment with ginseng may ameliorate these disorders by modulating adrenal function.
- One gram of Korean red ginseng extract (Korea Ginseng Corporation, Seoul, Korea) was given twice a day to children with ADHD in a randomized double blind placebo controlled study.
- The ginseng group had significantly decreased inattention/hyperactivity scores compared with the control group at week 8 and an increase on their theta/beta ratio on quantitative EEG (see section on neurofeedback) which improves ADHD symptoms. (Hasegawa et al, 2013).

- Side effects were minimal but can include, such thing as, diarrhea, agitation and headache.
-
- Risk factors
- Many of these preparations are purchased from Asia and are not inspected by the Federal Drug Administration and may have infiltrates. Caution is advised when using these compounds. More research is needed to determine if these products will be helpful and standardization and determination of safety of the products should be done

- Racetams
- There are three types of racetams.
- They are aniracetam, piracetam and pramiracetam. Piracetam is a GABA derivative (an excitatory neurotransmitter in the brain) that is thought to modulate neurotransmission in a range of transmitter systems (including cholinergic and glutamatergic), has neuroprotective and anticonvulsant properties, and improves neuroplasticity.
- In a double blind placebo controlled study of 225 children with dyslexia, piracetam (given in a dose of 3,000 mg/day, significantly improved reading and comprehension after 12 weeks. No significant side effects occurred (Zavadenko, et al, 2004).
-

- A newer randomized controlled study in children given 100 mg/ kg/day demonstrated positive effects on reading and spelling skills in 56% of children with dyslexia.
- They demonstrated improvements in fluency and accuracy of reading along with a significant decrease of specific errors (dysphonemic and visuospatial) in dictation.
- Interestingly, interhemispheric asymmetry in EEG alpha-theta-sub bands (4-13 Hz) was noted during the performance of incomplete figures recognition test in the piracetam treatment group.

- In a double blind placebo controlled study, the researchers reported significant effects of piracetam in enhancing letter detection and on event related potentials associated with letter hits.
- These results led to the conclusion that piracetam may increase the efficiency of left hemisphere areas associated with letter recognition. (Conners, et al, 1987)
- Many of these preparations are not inspected by the Federal Drug Administration and may have infiltrates. Caution is advised when using these compounds. More research is needed to determine if these products will be helpful and standardization and determination of safety of the products should be done.
- One resource may be found at www.smartnutrition.com

- Chelation
- A study using penicillamine in 44 hyperactive children with lead toxicity (lead \geq above 25 mcg/dL) was done. The study randomized the children to either placebo, methylphenidate or penicillamine.
- Penicillamine was more effective than placebo on teacher-rated hyperactivity and was nominally better than methylphenidate 5-40 mg (Dietrich. Et al 2004)
-
- Risk factors
-
- More research is needed. Unless there is documented lead toxicity, this method is not recommended due to safety concerns..

- Effect of media
- Unfortunately, electronics has been used by busy parents to keep kids entertained.
- However, in a longitudinal study of 1300 children, the best predictor of ADHD at age 7 was early exposure to TV.
- Those who watched TV for more than 5 hours per day had the greatest risk (Christakis, et al, 2004).
- However, in a longitudinal study of 1300 children, the best predictor of ADHD at age 7 was early exposure to TV.
- Those who watched TV for more than 5 hours per day had the greatest risk (Radesky, et al, 2014)

- In another study, 49 infants between 8 and 14 months of age, were randomized to either DVD watching or block playing.
- Those who watched DVD's for 45 minutes had higher salivary cortisol (an indication of stress).
- Exposure to electronics may also affect executive function.
- In a study of 60 four year olds, the children were exposed to either Sponge Bob, educational TV or drawing.
- For executive tests were performed and those who were exposed to Sponge Bob had a significant decrease in executive function (Lillard, et al, 2015).

- Electronic holidays may be important to future develop of children. In a randomized controlled study of 585 children age 3-5 years, educational and prosocial programs were substituted for aggression focused and high stimulating TV. Significant improvements in behavior and social competencies were noted 6 months later and no decline was noted 12 months out (3).

To test or not to test

- Genetic testing may help to identify:
- COMT
- MTHFR
- 2D6 slow metabolizers
- Potentiation for weight gain on atypical and typical antipsychotics
- CAC and ANK genes
- Other p450 genes

Summary

- These studies just covered ADHD.
- All of these studies need replication
- Most have small N's
- Although these studies open the door for further research, these studies are helping to help us note that CIM will likely play a role in the future of child psychiatry.
- More research is needed.