Brainclinics®
THE personalized medicine resource

Personalized Medicine & DSM-V

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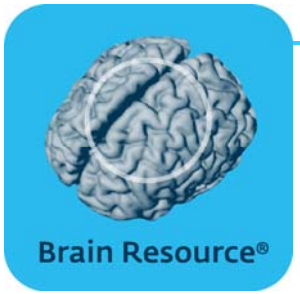


The Brain Resource Company (BRC)

First standardized International Brain Database

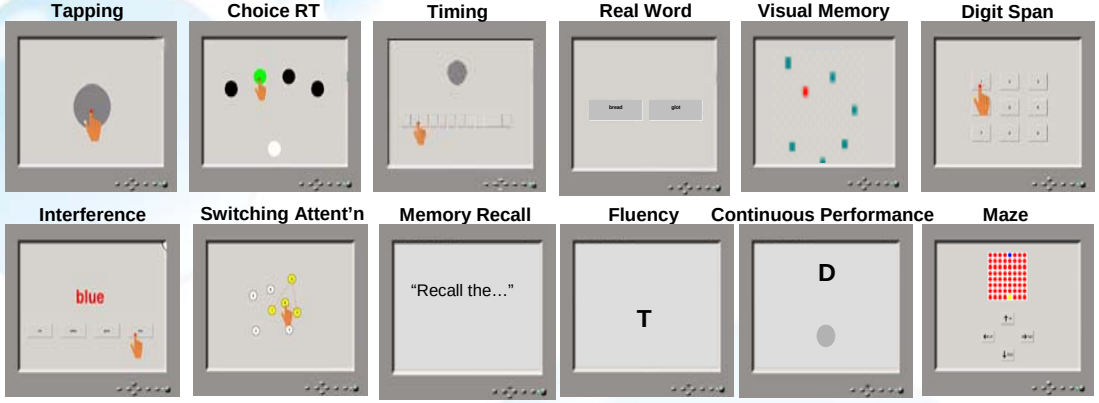
Over 100 labs, 120 scientists, 150 projects in USA, Europe, South Africa, Australia (over 100 publications)

A/Prof Evian Gordon - CEO
A/Prof Lea Williams – Director, Brain Dynamics Centre
Dr Chris Rennie – Physicist – Sydney University
Prof Peter Robinson – Theoretical physicist – Sydney University
Prof Ed Bullmore – Psychiatry – Cambridge University
A/Prof Richard Clark – Psychology – Flinders University
Prof Ruben Gur – University of Pennsylvania
Prof Jim Wright – Psychiatry – University of Auckland
Prof Peter Schofield – Prince of Wales Research Institute
A/Prof Robert H. Paul – Preventative Medicine, Rhode Island
Prof Ron Grunstein – Woolcock Institute of Medical Research
A/Prof Steven Silverstein – Rob. Wood John. Med. School, NJ
Prof Alexander McFarlane – University of Adelaide
Prof Evgeni Sokolov – University of Moscow
Prof Elkhonon Goldberg – Neurology – New York University
Prof Steve Williams – Neuroimaging – IoP, London

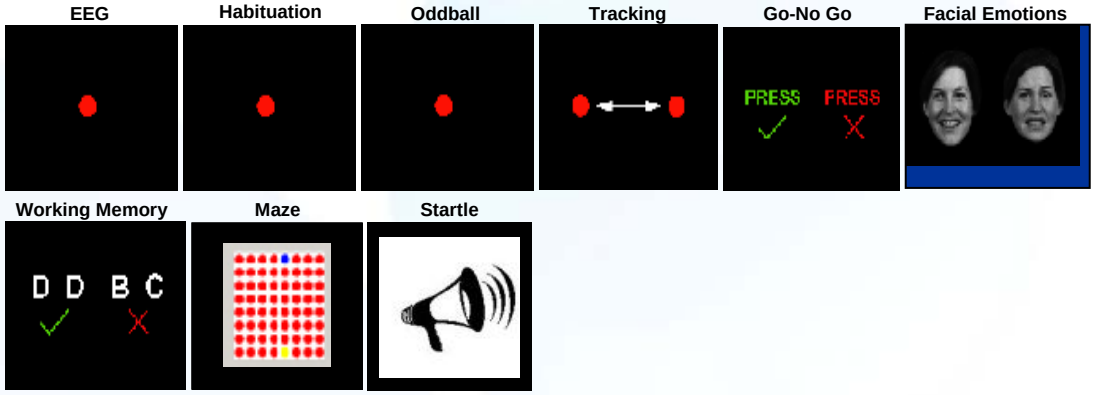
BRC database in a nutshell

- Currently > 20.000 subjects
- Standardization; multimodal (EEG, ECG, Respiration, GSR, EOG, neuropsychology, clinical tests)
- DNA, fMRI, sMRI
- Automated and objective data processing

Neuropsychological Test Battery (Cognition)



Electrical Brain Function



sMRI and fMRI

sMRI: MPRAGE, Dual Echo, Diffusion Tensor Imaging (DTI)

fMRI: Auditory Oddball, Go-No Go, Face Emotion Processing, Working Memory

Genetics

Cheek swab and blood samples

In addition:

- 22 Web demographics (EQ, medication use, Depression, Anxiety, Stress, medical history, sleep etc.)
- NEO-FFI: Big five personality scale (neuroticism, extarversion etc.)

Psychophysiological Activation Tasks

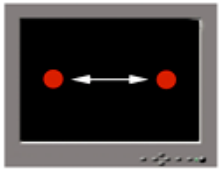
Measures of electrical brain function over fractions of a second time scale.

Brain (EEG and ERP) and body measures (of arousal, heart rate, respiratory rate) are undertaken simultaneously using non-invasive recording discs placed on the scalp and skin.

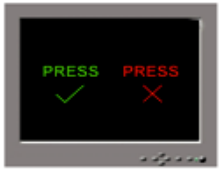
Resting EEG
Baseline eyes open and eyes closed.

Habituation
Listens passively to repeated auditory stimuli (automatic learning).

Auditory oddball
Differing tones and press a response button to infrequent high tones (process relevant whilst ignoring irrelevant information).



Visual tracking
Track red dot moving horizontally at 0.4Hz (automatic visual tracking).

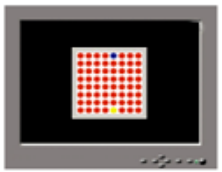


Go–No Go
Press a response button only when they see the word "PRESS" in green (suppressing well-learned, automatic responses).

Conscious and subconscious processing of facial emotions
Rate a range of facial expressions (processing emotions).

Visual working memory
Press a response button when the same letter appears twice in a row (sustained attention and working memory).

Executive maze
Discover (by trial and error) a hidden path through the maze and remember it (planning, foresight, error correction and memory).

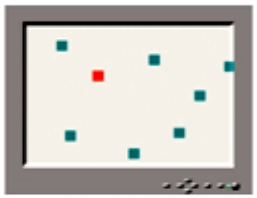


Startle
A series of loud tones (the "fight or flight" response).

IntegNeuro - Cognitive Tasks

Motor tapping
Tap the circle as fast as possible (manual dexterity).

Timing
A circle appears on the screen and the subject is required to indicate the correct duration (time estimation).



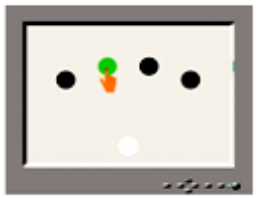
Span of Visual Memory
Press a series of squares on the screen in the order in which they previously lit up (spatial working memory capacity).

Verbal Interference
Name the 'ink' colour a word is written in (suppress unwanted, well-learned automatic responses).

Memory Recall and Recognition
Recall and recognize a set of words after various time intervals (memory).

Malingering
Description withheld (validity of deceptive claims of memory impairment).

Choice reaction-time
Press the lit circle as quickly as possible (reaction time).



Spot The Real Word
Select the real rather than nonsense word (language comprehension).

Digit span
Repeat a sequence of digits in either forward or backward order (working memory).

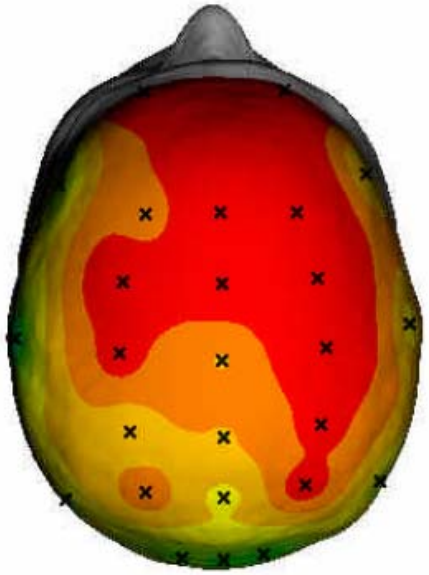
Switching of Attention
Numbers and letters are connected up in various sequences (ability to shift the course of mental activity).

Word Generation
Say as many words as possible which start with a given letter (verbal fluency).

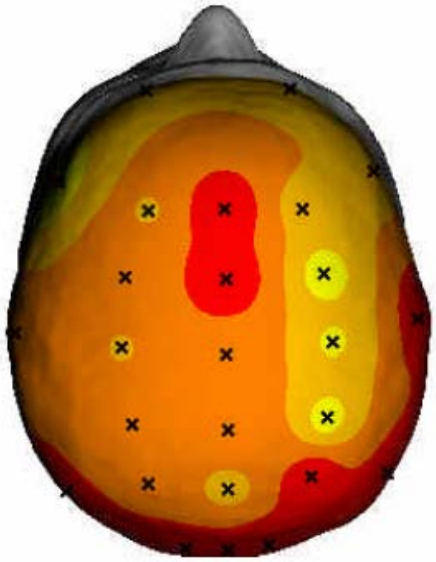
QEEG

Example: ADHD

Brain Function
EEG Theta Marker



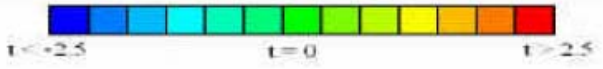
AVERAGE data:



Raised EEG Theta power (figure above), most pronounced frontally, $p < .0001$
Raised EEG relative Theta (figure left) in eyes open/closed conditions

Raised EEG Delta power also observed.

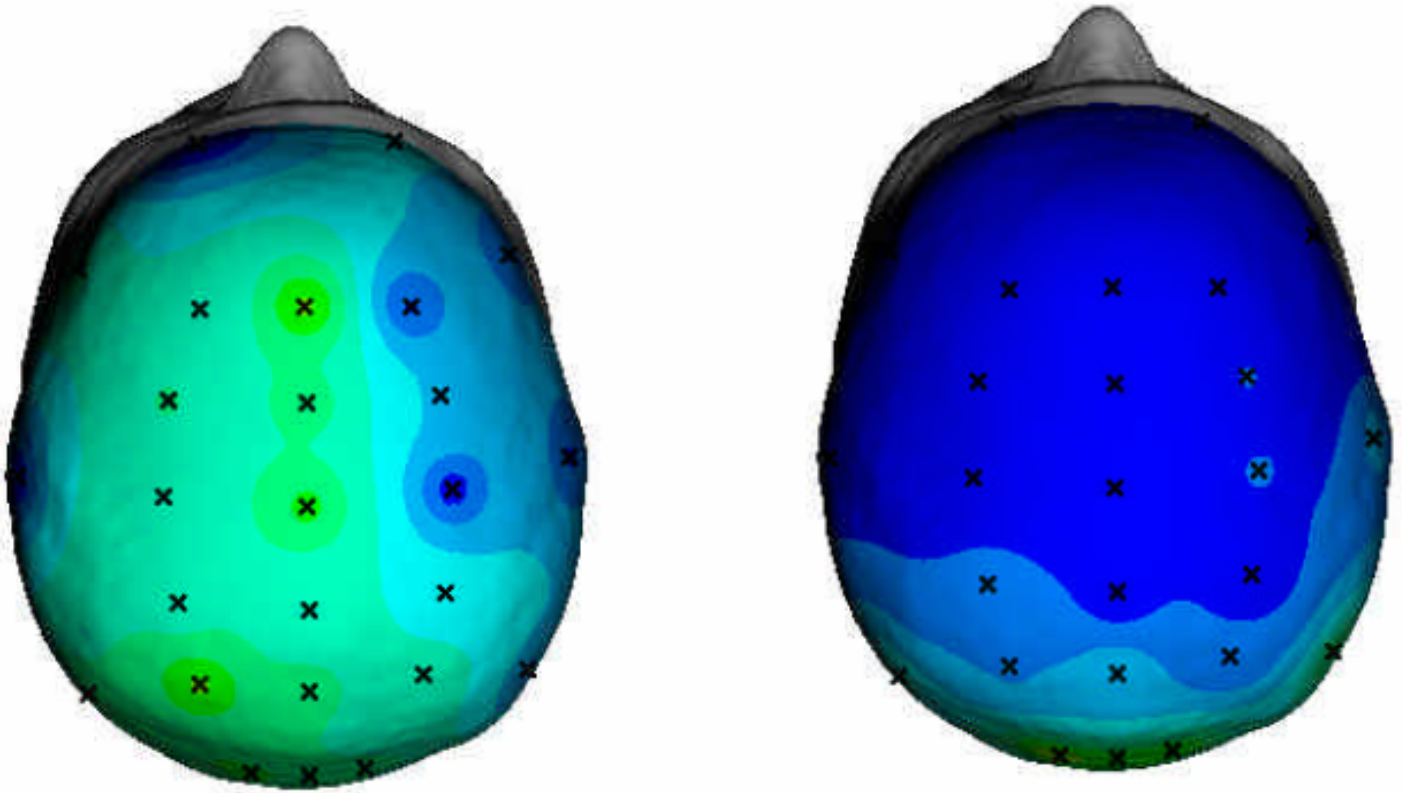
Compared to Matched Controls



Key: Warmer colors (with positive t values, right) indicate greater Theta compared to controls, while cooler colors indicate less Theta.

Beta power showed a significant **reduction** in ADHD – most apparent fronto-temporally

This finding is consistent with cortical arousal dysregulation in ADHD – and complements the findings for EEG Theta



Reduced EEG Beta power (figure left) and EEG relative Beta (figure right).
Most pronounced right fronto-temporally, $p < .0001$
in eyes open/cosed condition

ADHD

INDIVIDUAL data:

Subtypes

50% have increased theta

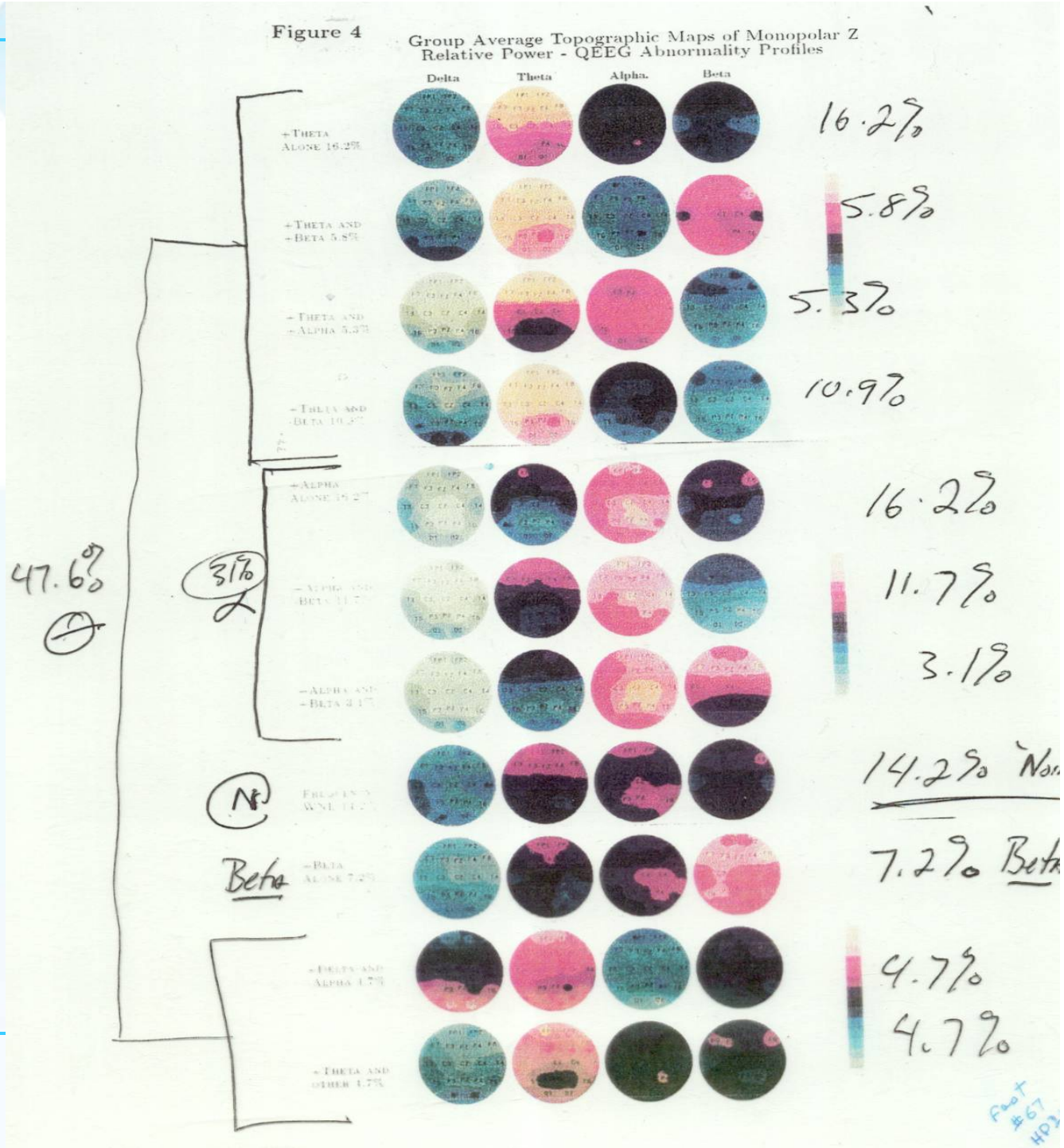
25% have <u>increased</u> Beta

Only <u>2 decreased</u> Beta!!!

ADHD: Brain Function - Cognition Profile

	theta	alpha	beta	P3	RT	Time	SoVM	VI	MR	SOA	WG	DS	CPT
2014	↑	↑			→			*				↓	*
2193	↑		↑	→				*		↑		↓	
2306		↑		→			↓	*			↓		
2395		→						*	↓	↑			
2418		↑								↑		↓	
2520		↑		←					↓				
2553	↑	←		→	→	↑	↓			↑		↓	*
2575				←				*			↓		
2744	↑	←↓	↑	→↓	→	↑		*	↓	↑			
2777	↑						↓		↓		↓		*
3149		↑			→		↓	*	↓	↑	↓		*
3251	↑	↑				↑							
3330	↑	↑		↑		↑		*	↓	↑	↓	↓	*
3521								*	↓		↓	↓	
3532				→					↓	↑			
3576	↑	←↑		→	→		↓	*	↓	↑		↓	
3813		↑						*		↑			*
3846	↑	↑	↑	→			↓	*		↑			*
3824											↓		*
3857	↑	↑		→				*			↓	↓	*
4061					→	↑		*		↑	↓		*
4151	↑		↑	→↓	→		↓	*		↑			*
4162	↑	↑	↑	→					↓	↑			
4409	↑			↑							↓		
4397		→	↓					*					
4465								*					*
4476		↑		↑	→				↓				
4487	↑	→↑	↑		→			*	↓			↓	*
4926		↑					↓		↓			↓	*
5163		→	↑	→	→		↓	*	↓				*
5118	↑	↑		→↓		↑	↓		↓				*
5208		↑			→		↓			↑		↓	
5400	↑	↑											
5411		↑	↑	→↓	→				↓	↑			
5422	↑	←	↓	→	→	↑	↓	*	↓			↓	
5332		←					↓	*					

ADHD
Subtypes



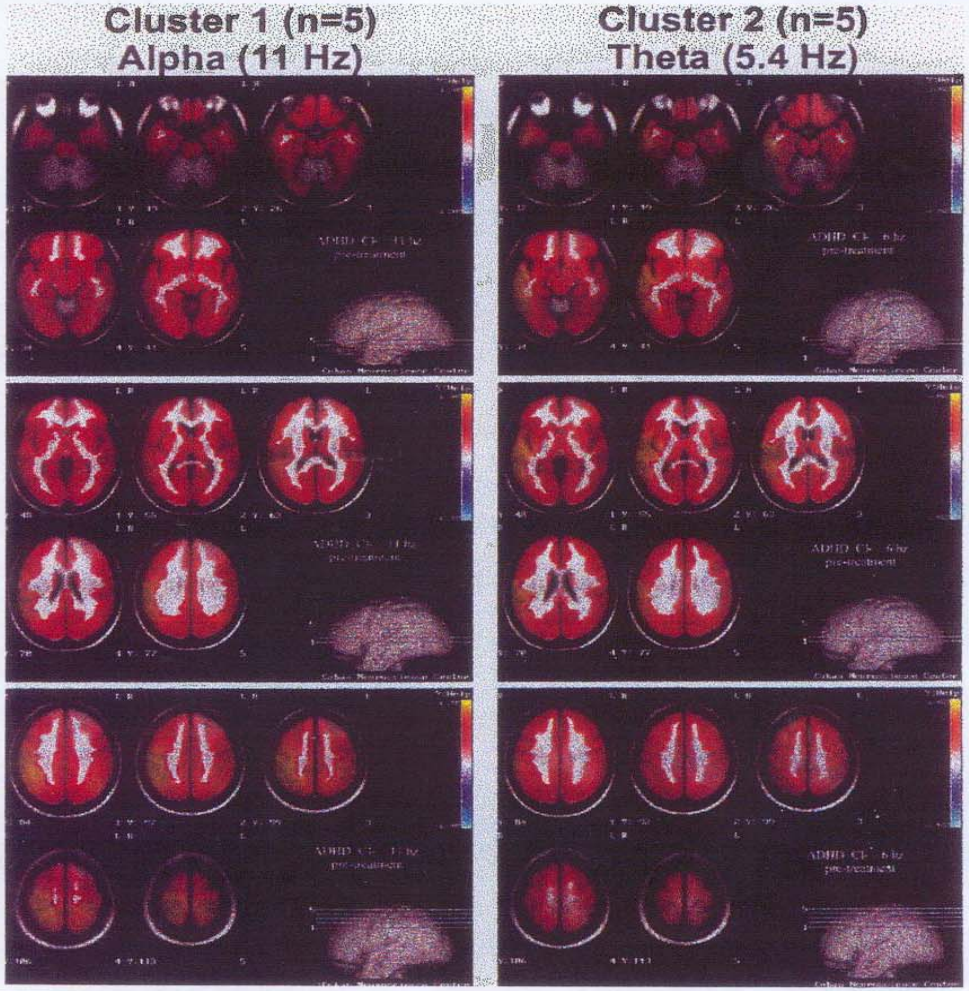
ADHD

Subtypes

E. Roy-John

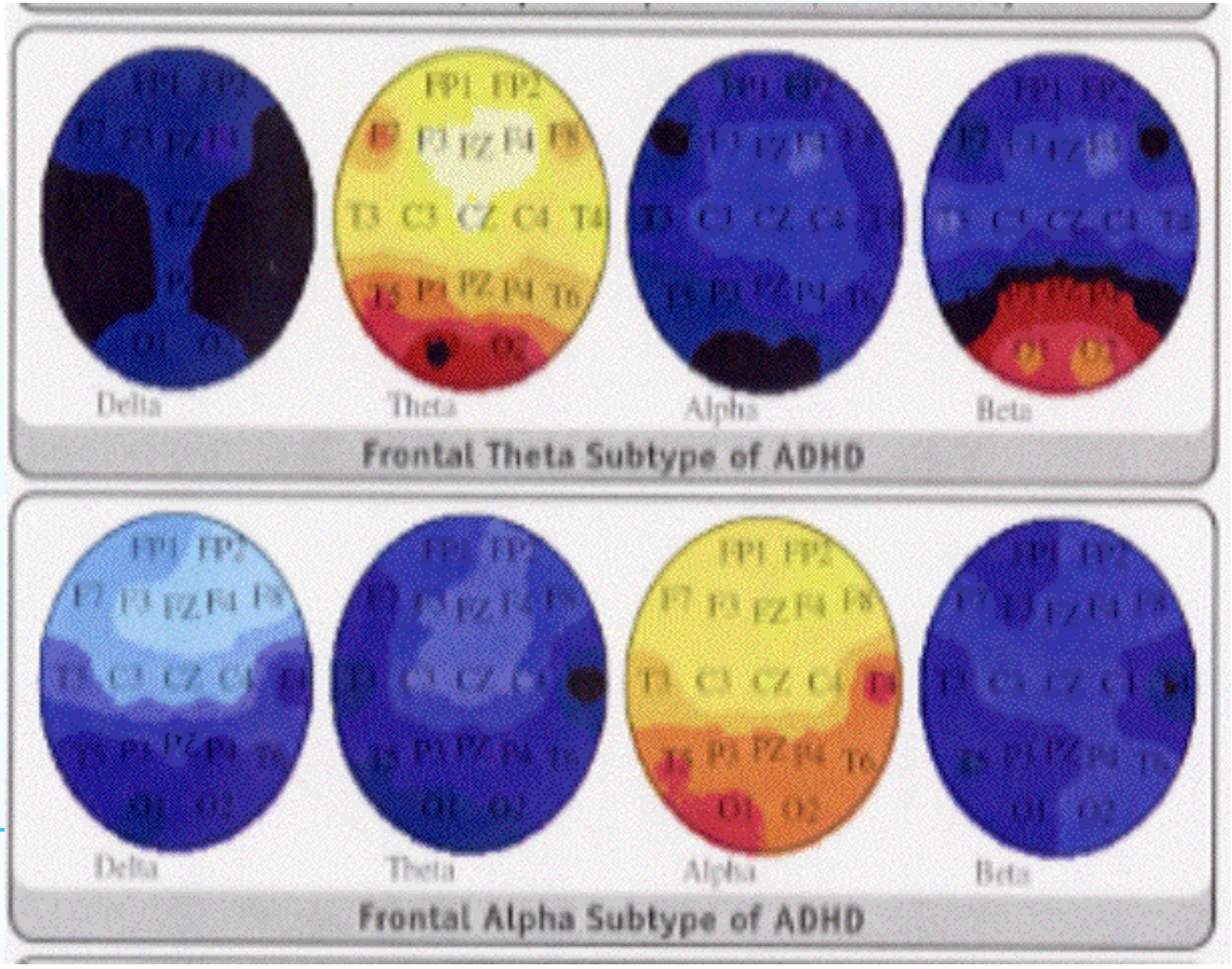
FIGURE 1. Quantitative EEG variable resolution electromagnetic tomography (QEEG VARETA) 3D images for two clusters of attention deficit disorder patients with different long-term responsiveness to stimulants. These images at narrow-band frequency values were selected because they reflect the maximal differences between cluster 1 (left panels, at 11 Hz) and cluster 2 (right panels, at 5.4 Hz). At each selected frequency, the average VARETA for the 5 patients closest to the centroid of cluster 1 and cluster 2 are shown. The corresponding panels for cluster 1 patients at 5.4 Hz and cluster 2 patients at 11 Hz fell within normal limits and are not presented. Images associated with cluster 1 show primarily cortical abnormalities (seen most clearly in the bottom panel on the left) that are maximal and that appear to originate in the right parietal cortical region. Images associated with cluster 2 show primarily temporal cortical and hippocampal abnormalities (seen most clearly in the top and middle panels on the right).

The three panels in each set present four transaxial VARETA images in 7-mm slices as depicted in the brain model in the bottom right portion of each panel. These 7-mm slices start at the base of the brain (top panels) and progress through the middle of the brain (middle panels) to the top of the brain (bottom panels). Color coding is in standard deviation units, with white representing normal activity, red to yellow shades excess activity, and purple to light blue a deficit of activity. The VARETA software was developed by Dr. P. Valdes-Sosa and colleagues at the Cuban Neuroscience Center.55 The superimposition of sources uses the probabilistic MRI atlas software developed by Dr. A. C. Evans and colleagues at the Montreal Neurological Institute.54



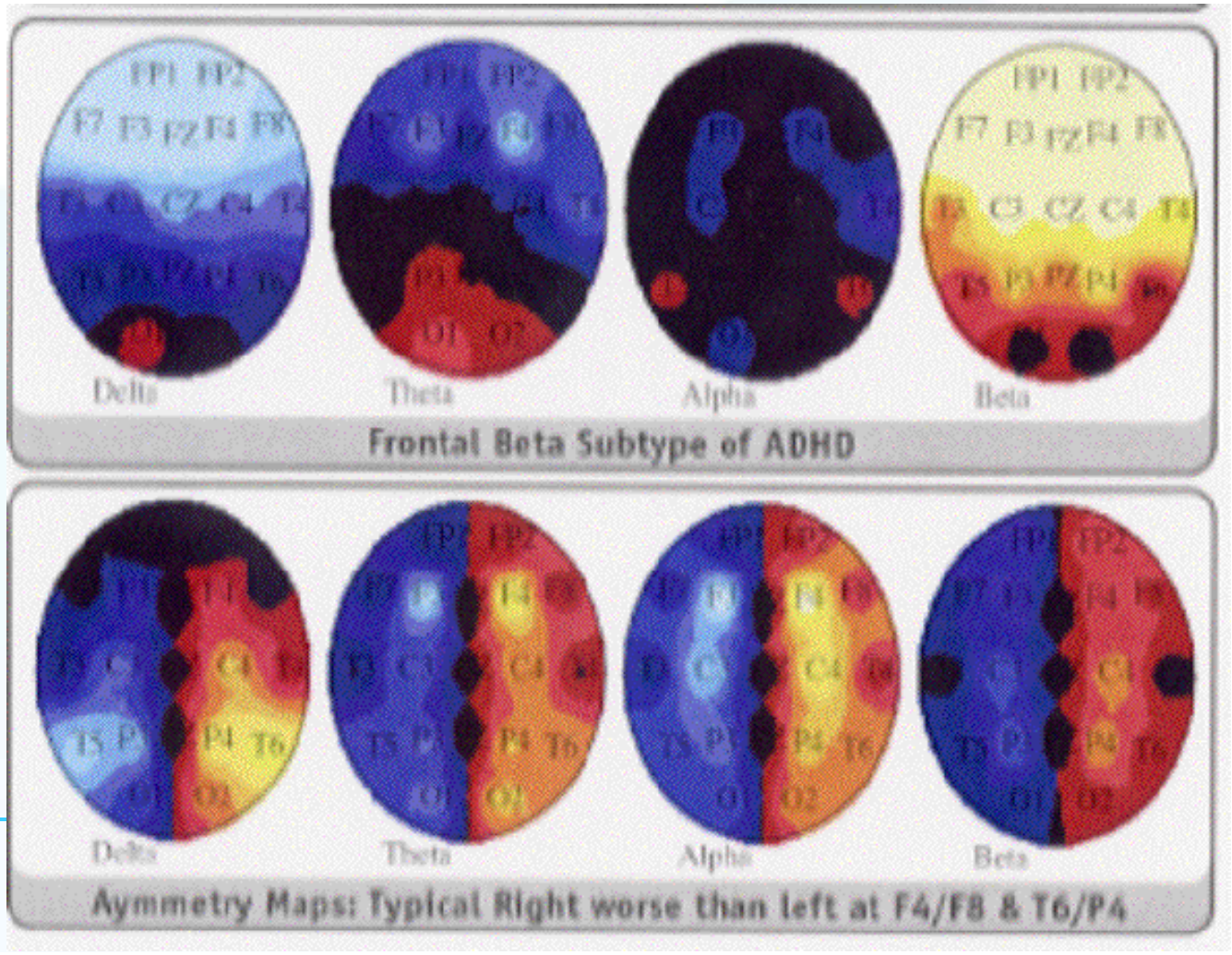
ADHD

Subtypes



ADHD

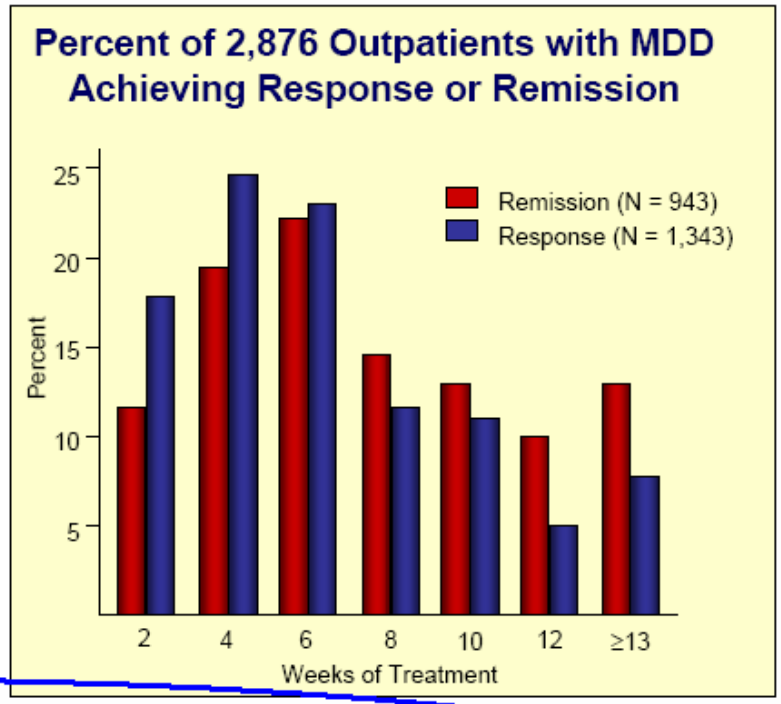
Subtypes



Major unmet medical need in depression
Example STAR*D study

- Effectiveness of SSRI (citalopram) in Patients with Major Depression (STAR*D study) Trivedi et al. (2006) Am. J. Psychiatry 163: 28-40

- *The STAR*D study shows:*
  - *Low remission rates (28% for HAM-D, 33% for QIDS-SR) with citalopram (exit dose 41.8 mg/day).*
  - *Comparable remission and response rates in primary and psychiatric care.*
  - *Better remission associated with higher socioeconomical status.*
  - *Long time to response or remission (~ 35% and 50% ≥ 8 weeks of treatment).*



➡ ~ 70% of patients do not respond adequately
➡ High clinical need for ADPs with better efficacy and faster onset of action

Medication response: ADHD and Depression

Table 1

Neurometric subgroups in attentionally and affectively disordered patients

DSM-III-R Diagnostic Categories	Neurometric Subgroups Characterized by Frontal Alpha excess	Other	Frontal Theta excess
Attentionally disordered	25 [54%]	7 [15%]	14 [31%]
Affectively disordered under age 18	18 [72%]	4 [16%]	3 [12%]
Affectively disordered age 18 and older	17 [59%]	8 [28%]	4 [13%]

Suffin & Emory, 1995

Medication response: ADHD and Depression

Suffin & Emory, 1995

Table 4

Pharmacoresponsivity of normocoherent clinical populations

	Neurometric Subgroups Characterized by Frontal Alpha excess responsive to antidepressants	Neurometric Subgroups Characterized by Frontal Theta excess responsive to stimulants
affectively disordered	9/10 [90%]	0 [0%]
attentionally disordered	13/15 [87%]	7/7 [100%]

Table 5

Pharmacoresponsivity of hypercoherent clinical populations

	Neurometric Subgroups Characterized by Frontal Alpha excess responsive to anticonvulsants/ lithium	Neurometric Subgroups Characterized by Frontal Theta excess responsive to anticonvulsants
affectively disordered	17/20 [85%]	2/2 [100%]
attentionally disordered	5/5 [100%]	2/3 [67%]

What is Personalized Medicine?

Current Practice

Trial and error

Personalized Medicine

The right treatment for the right person at the right time

DSM-IV vs. DSM-V

DSM IV	DSM's Future 2011 ?
Axis I: Clinical syndromes and disorders Classic psychiatric disorders such as depression or complaints such as relationship problems	**Axis I: Genotype** Genes linked to diseases, symptoms, resiliency, and drug response
Axis II: Personality disorders and mental retardation Disorders characterized primarily by long-standing traits	**Axis II: Neurobiological phenotype** Cognitive abilities, emotional regulation, brain-imaging profile, and other qualities
Axis III: General medical conditions Any non-mental disorder that might influence mental health	**Axis III: Behavioural phenotype** Expression of disease-related behaviours, including their range and frequency
Axis IV: Psychosocial problems Includes loss of job, homelessness, and other factors that contribute to the other axes	**Axis IV: Environmental modifiers or predictors** Environmental factors that alter the neurobiological or behavioural phenotype
Axis V: Global assessment of functioning An overall rating of the patient's social pro	**Axis V: Therapeutic targets and response**

A diagnosis is more than a label, it directs successful treatment

Multiple Genes associated with each disorder

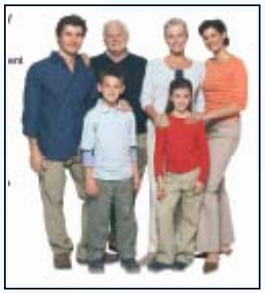
Disorder	Genetic Markers	References
MCI/ Alzheimer's	• *APOE ε4*	Saunders, 1993
	• *A2M 5 bp del (intron 17)*	Blacker, 1998
	• *LRP1*	Verpillat, 2001
	• *PSI & PS2*	Pericak-Vance, 2000
	• *APP*	Pericak-Vance, 2000
	• *BDNF Val66Met (Met allele)*	Kunugi, 2001
Depression	• *5HTT (Short allele)*	Caspi, 2003
	• *BDNF Val66Met (Met allele)*	Jiang, 2005
	• *HTR1A -1019 G*	Lemonde, 2003
	• *TPH2 441 His*	Zhang, 2005
	• *MTHFR 222 Val*	Lewis, 2006
	• *CRHR1*	Licinio, 2004
Schizophrenia	• *Dysbindon (DTNBP1)*	Straub, 2002
	• *Neuroregulin (NRG1)*	Stefansson, 2002
	• *DISC1*	Hennah, 2003
	• *COMT Val$^{108/158}$Met (Val allele)*	Egan, 2001
	• *RGS4*	Chowdari, 2002
	• *DAOA*	Chumakov, 2002
ADHD	• *DAT1 (10-repeat allele)*	Lim, 2006
	• *DRD4 VNTR 7R*	Faraone, 2001
	• *DRD5 148 bp (prom)*	Lowe, 2004
	• *SLC6A3 VNTR 10R*	Faraone, 2005
	• *COMT Val$^{108/158}$Met (Val allele)*	Eisenberg, 1999
	• *5HTT (Long allele)*	Kent, 2002

Illustrative Examples of Genomic-Neuromarker Predictors of Treatment Response in Depression

Genomic-Neuromarker	Drug	Predicted Rx Reponse	No. of Patients	Reference
BDNF	Citalopram	BDNF (Met-allele) better response	83	Choi et al., (2006)
5HTTLPR	Fluoxetine	Poorer response	36	Perlis et al., (2003)
COMT	Mirtazapine	COMT (Met/Met) poor response to mirtazapine (but not paroxetine)	102	Szedegi et al., (2005)
Alpha Asymmetry	Fluoxetine	Nonresponders greater R>L asymmetry	53	Bruder et al., (2001)
EEG Alpha	Variety	Excessive alpha favourable response	100	Suffin & Emory, (1995)
EEG Theta	Citalopram or Reboxetine	Increased Theta response	20	Mulert et al., (2007)
EEG Theta	Imipramine	Lower pre-treatment, but higher post-treatment positive response	40	Knott et al., 1996
EEG Cordance	Fluoxetine	Distiguishes treatment response	24	Cook et al., (1999)
LDAEP values	Citalopram	Higher LDAEP in responders	20	Mulert et al., (2007)
Grey matter volume (ACC)	Fluoxetine	Greater ACC faster improvement	17	Chen et al., (2007)
Rostral ACC metabolism	SSRI or Tricyclic or Bupropion	ACC hypermetabolism better outcome	18	Mayberg et al., (1997)

COMBINATION of Genes+Brain

- The effect of genes (genomics/proteomics) on behavior is not direct and is mediated via the brain.



Phenotype

Endophenotype

+

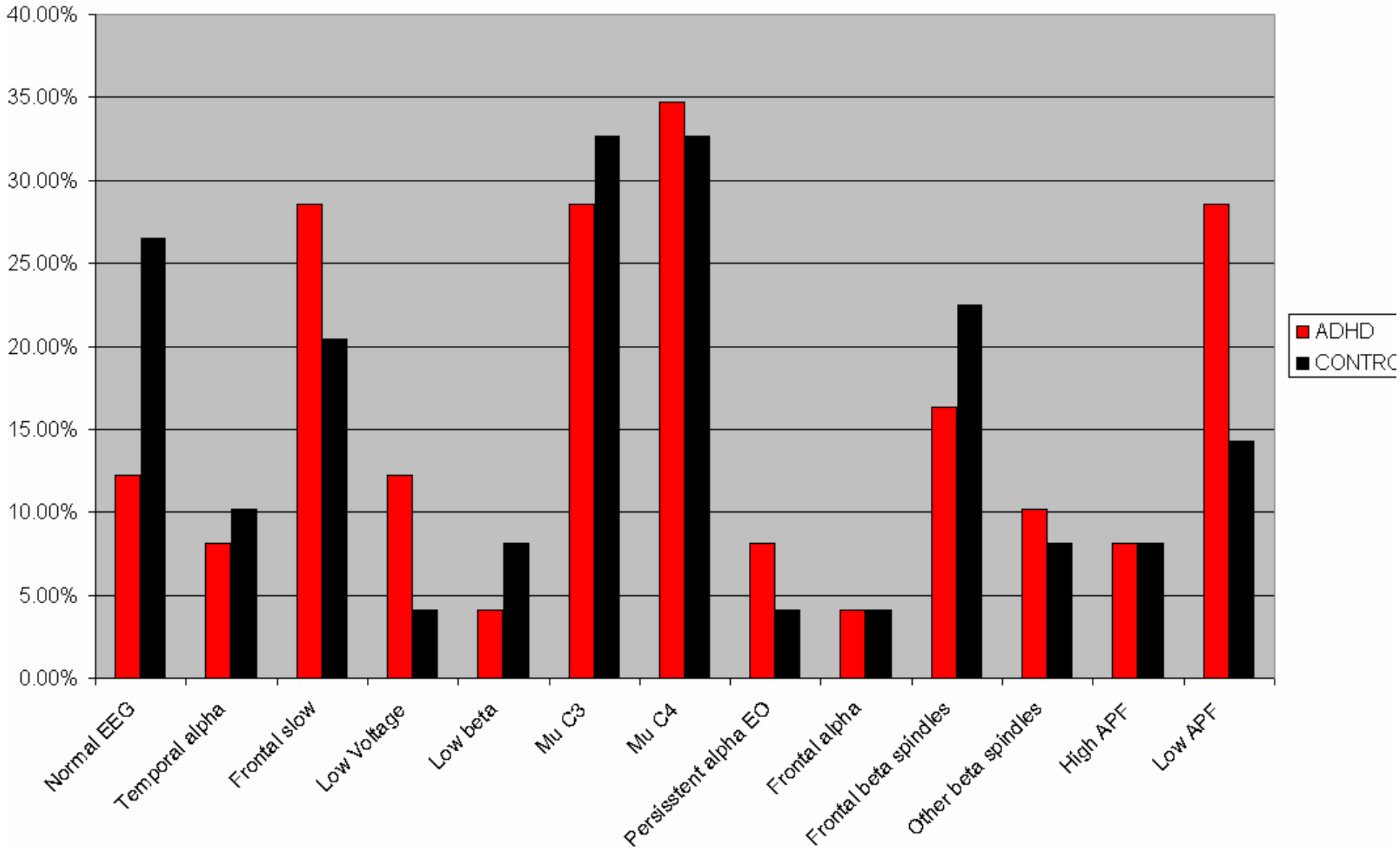
Genotype

EEG Phenotypes (Johnstone, Gunkelman et al., 2005)

Correlations between EEG frequency and metabolic rate!

- Diffuse slow activity, with or without low frequency alpha
- Focal abnormalities, not epileptiform
- Mixed fast and slow
- Frontal lobe disturbances
- Frontal Asymmetries
- Excess temporal lobe alpha
- Epileptiform
- Faster alpha variants, not low voltage
- Spindling excessive beta (example)
- Generally low magnitudes (fast or slow)
- Persistant alpha with eyes open (example)

Prevalence of different EEG Phenotypes in 50 children with ADHD vs. 50 matched healthy controls



Beta spindles

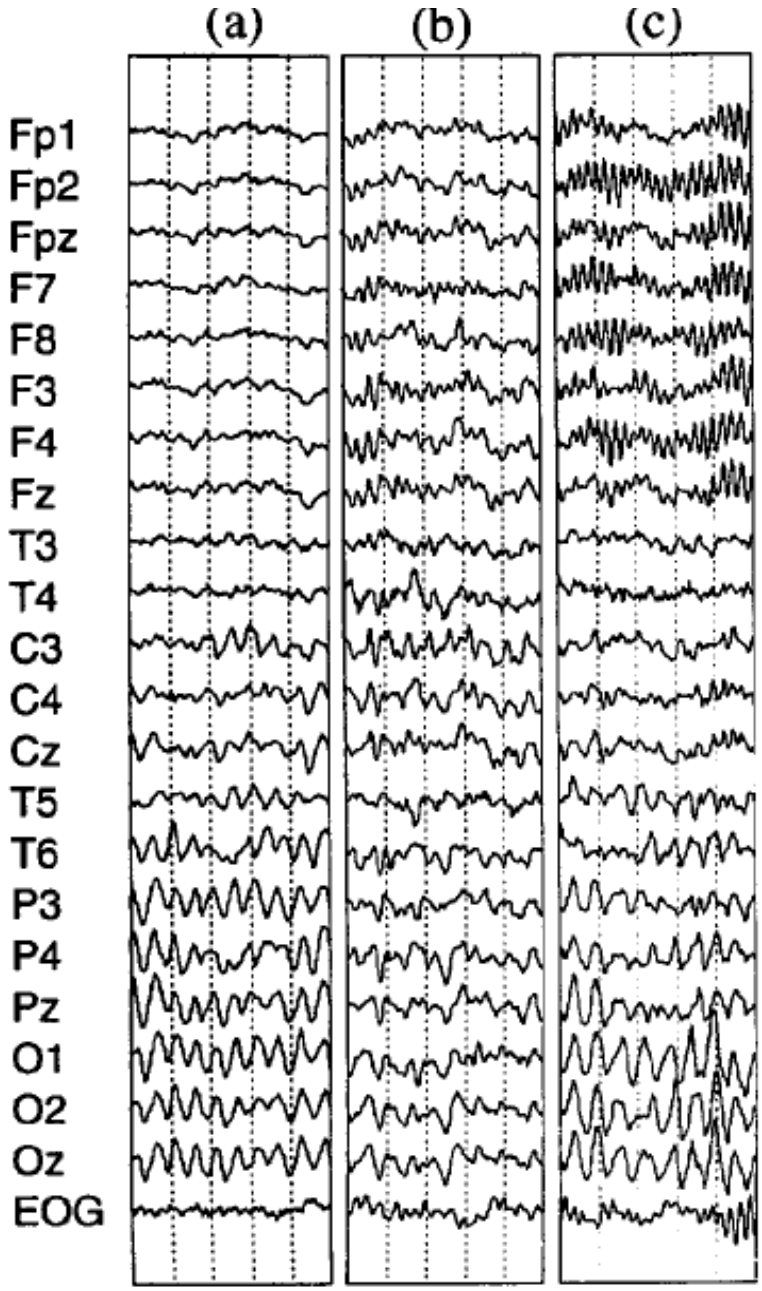
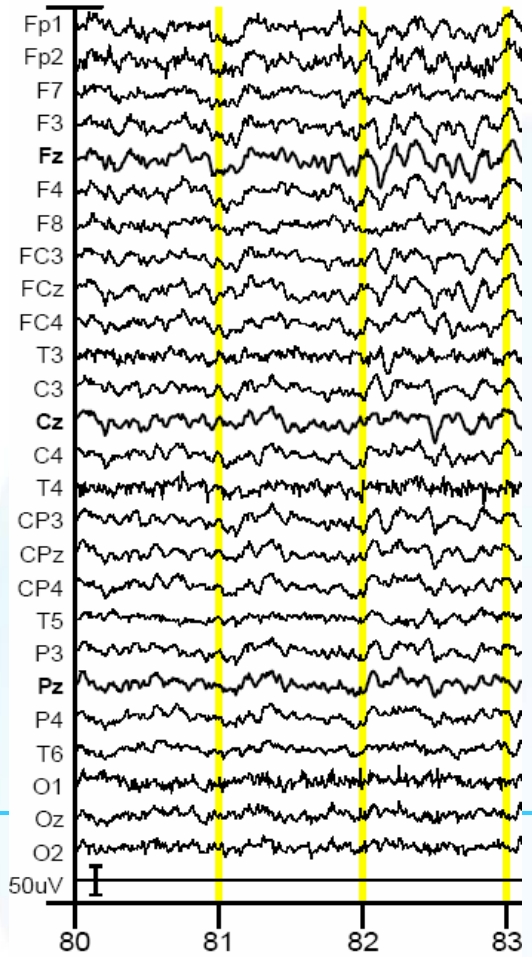
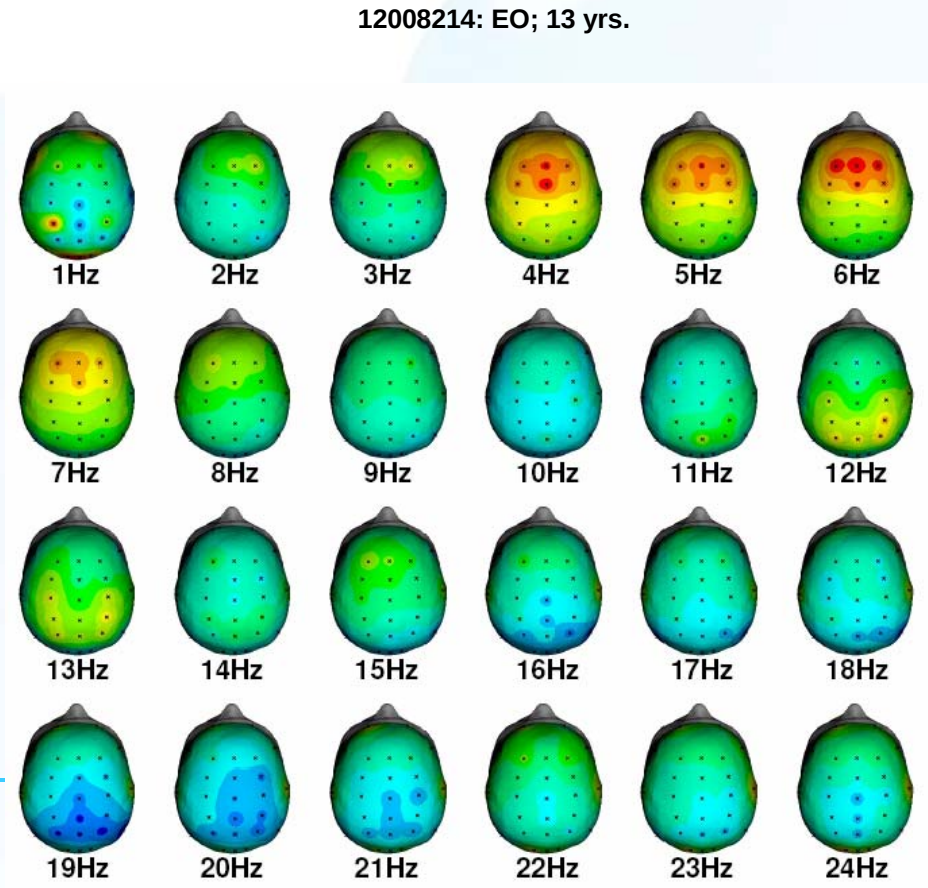


Fig. 1. Representative 1-s epochs from: (a) normal amplitude excess beta subjects; (b) high amplitude excess beta subjects; (c) excess beta subjects with frontal beta spindles.

Clarke et al., 2001

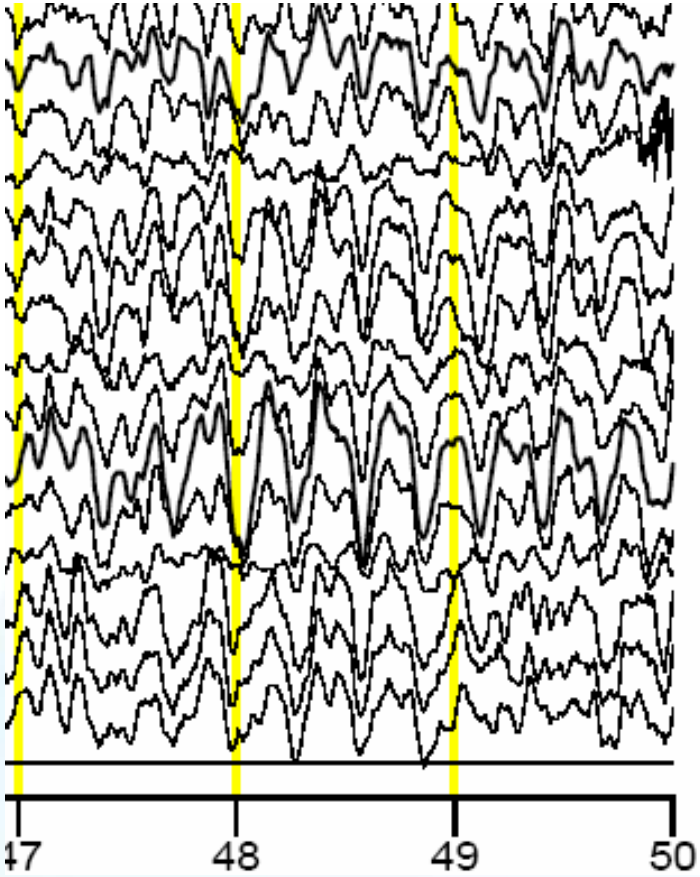
Frontal Disturbances: Theta



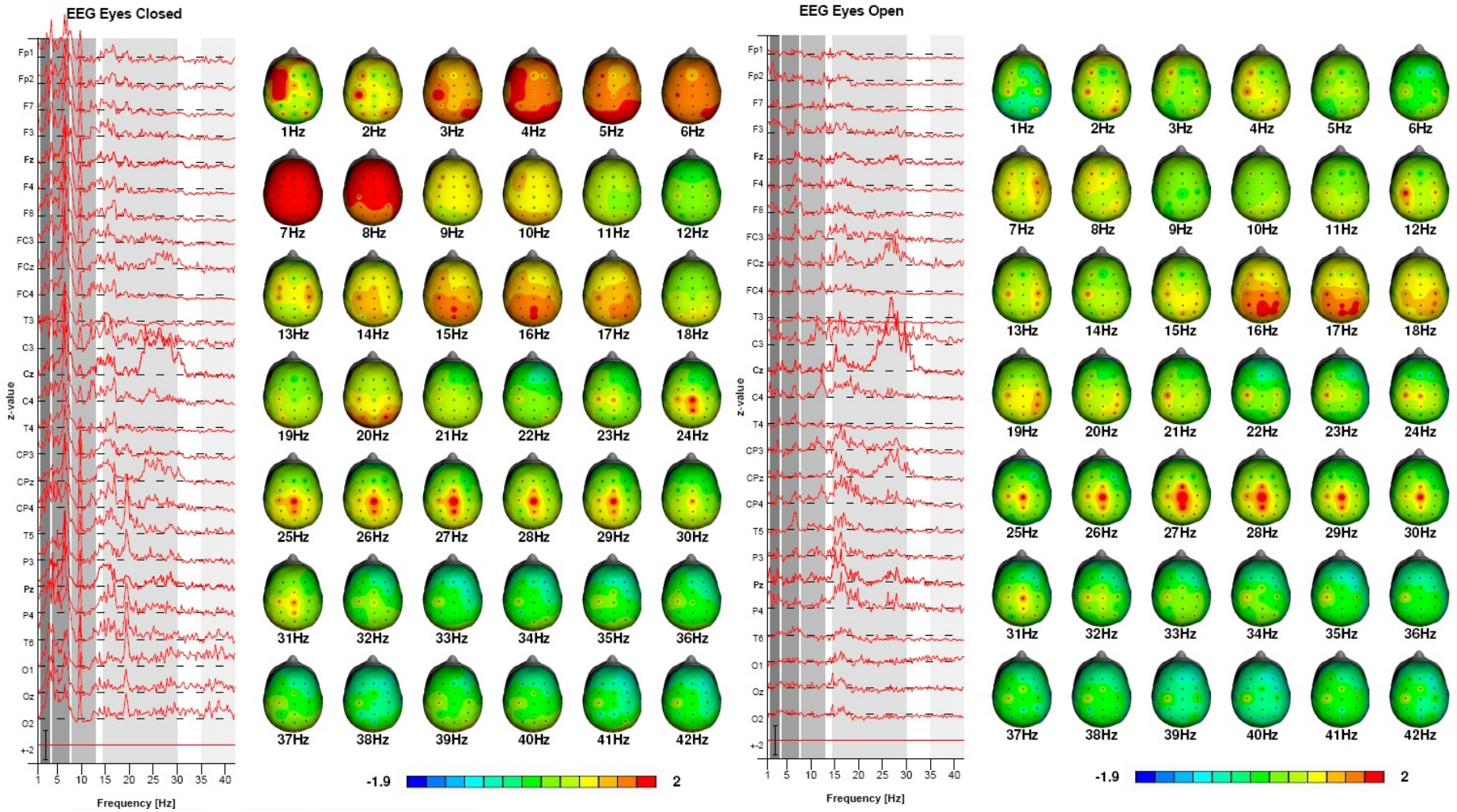


Know what is normal and what is not…

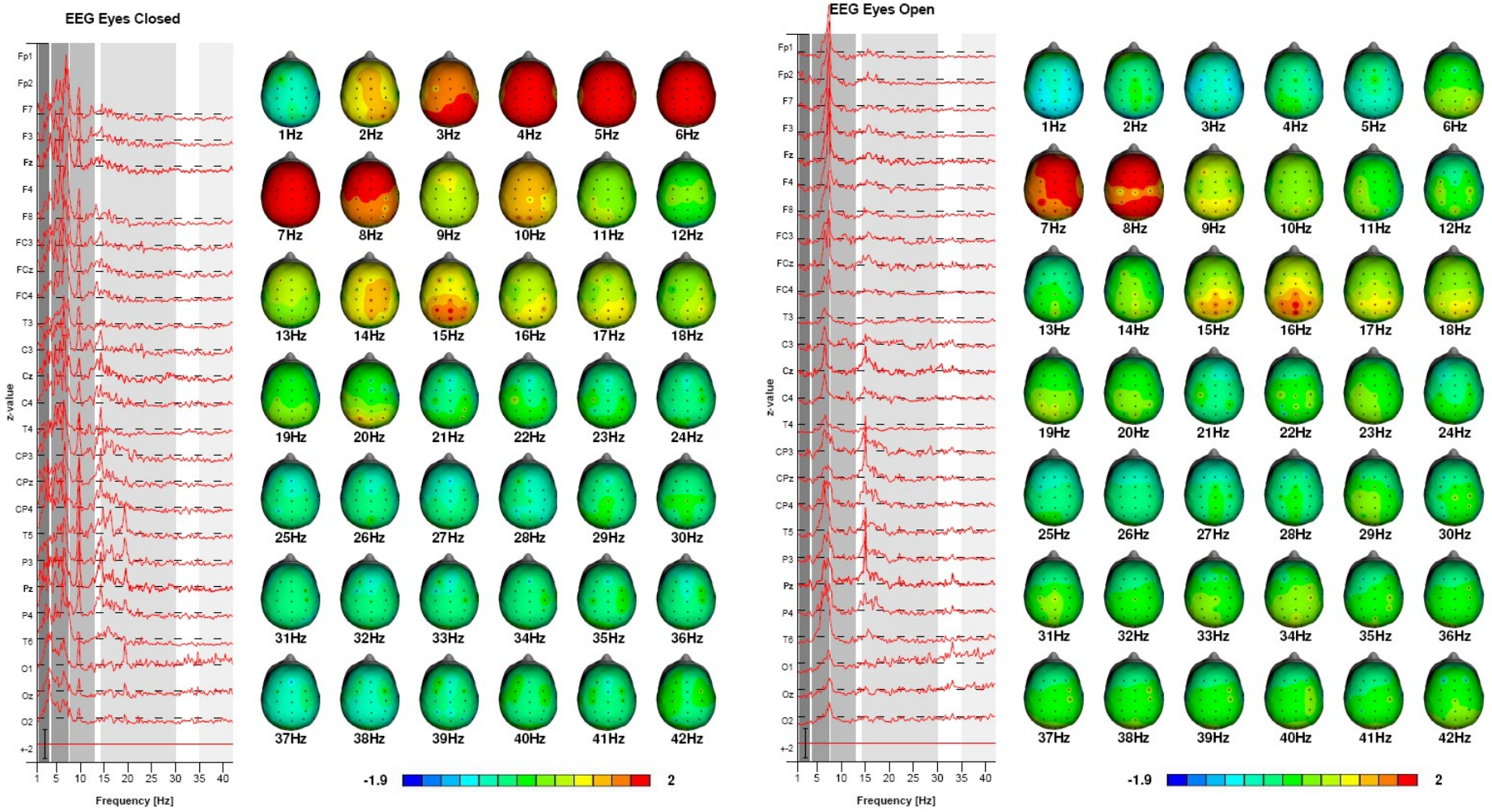
10022915: EC; 7 yrs. Inattentive problems.



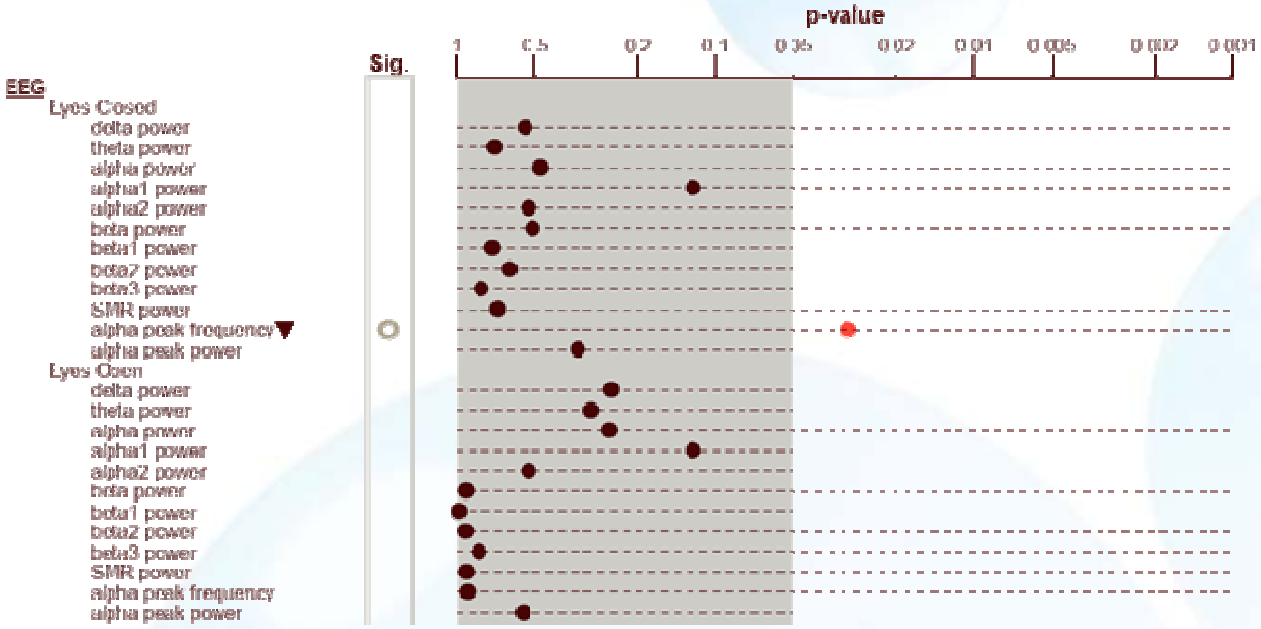
ADHD: frontal slow and beta spindles PRE-TREATMENT (NF)

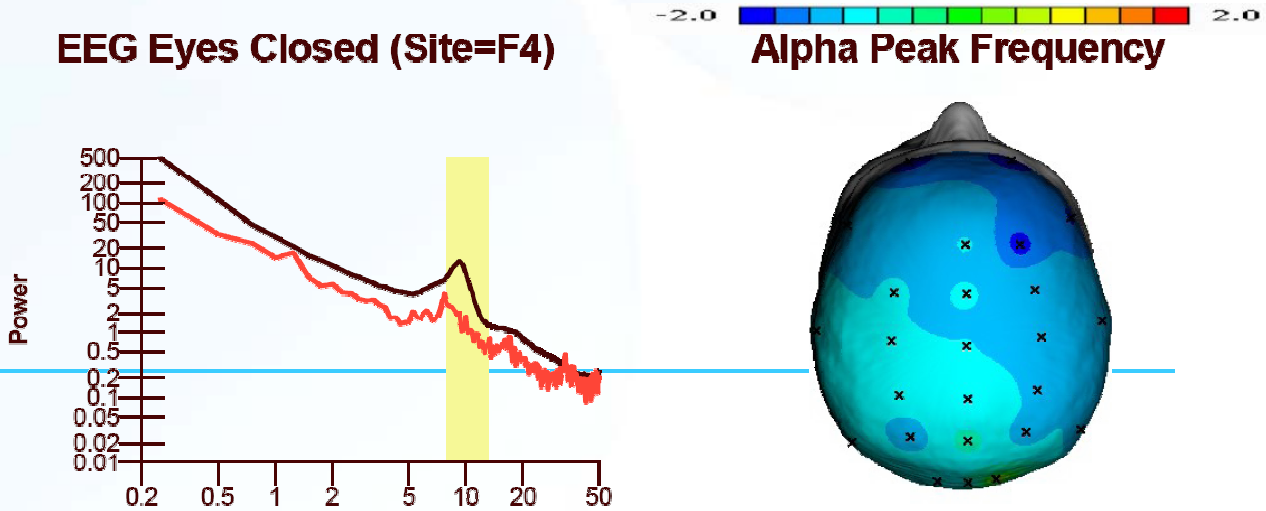


ADHD: frontal slow and beta spindles POST-TREATMENT (NF)

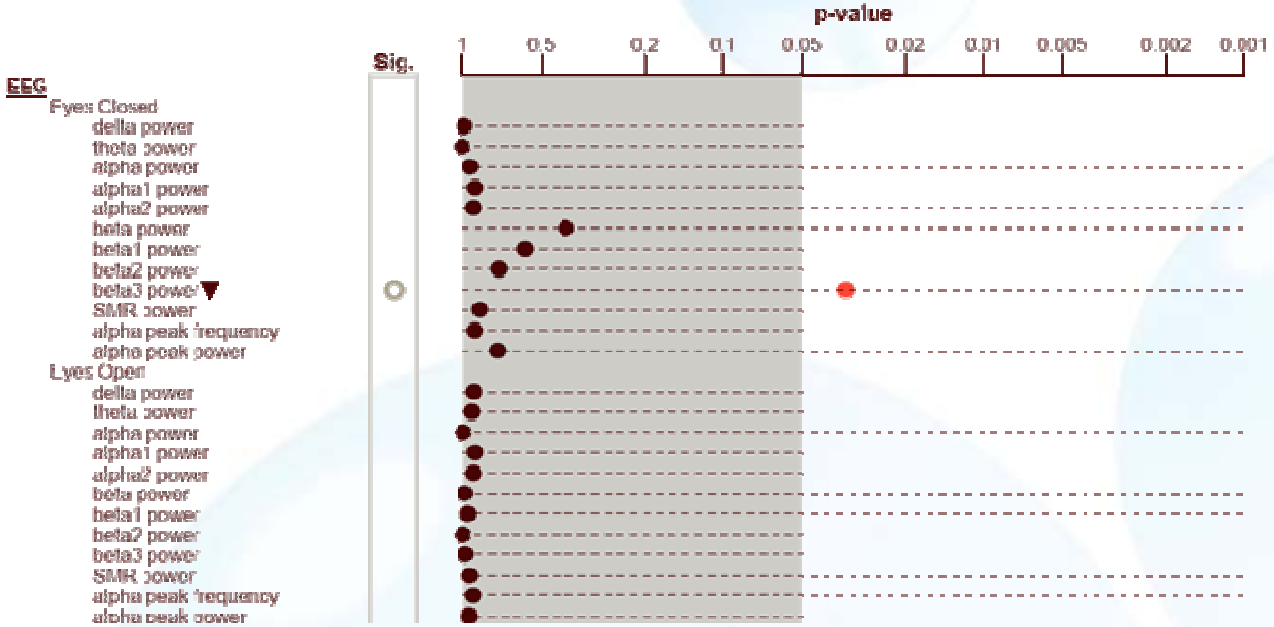


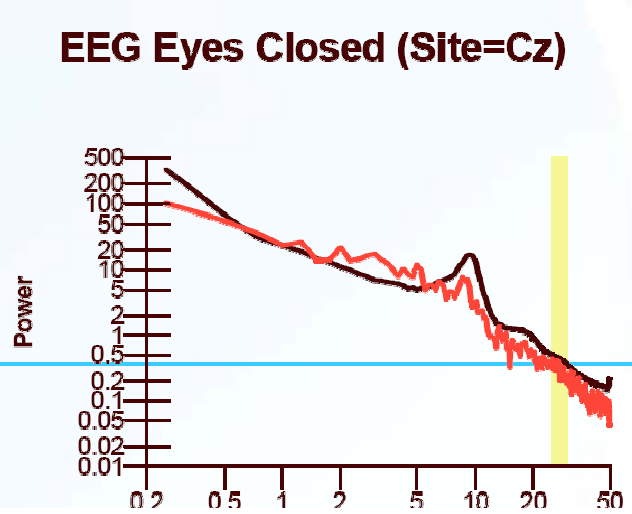
TBI pre-treatment QEEG

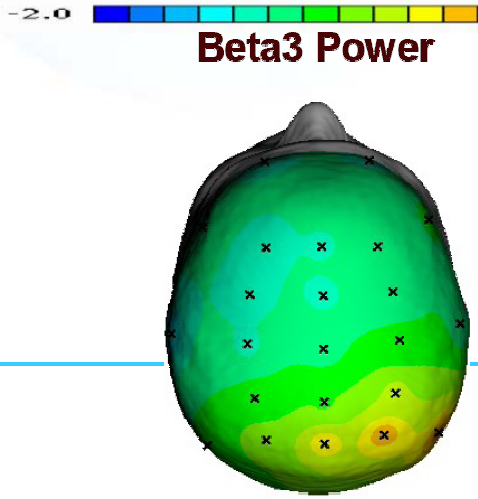




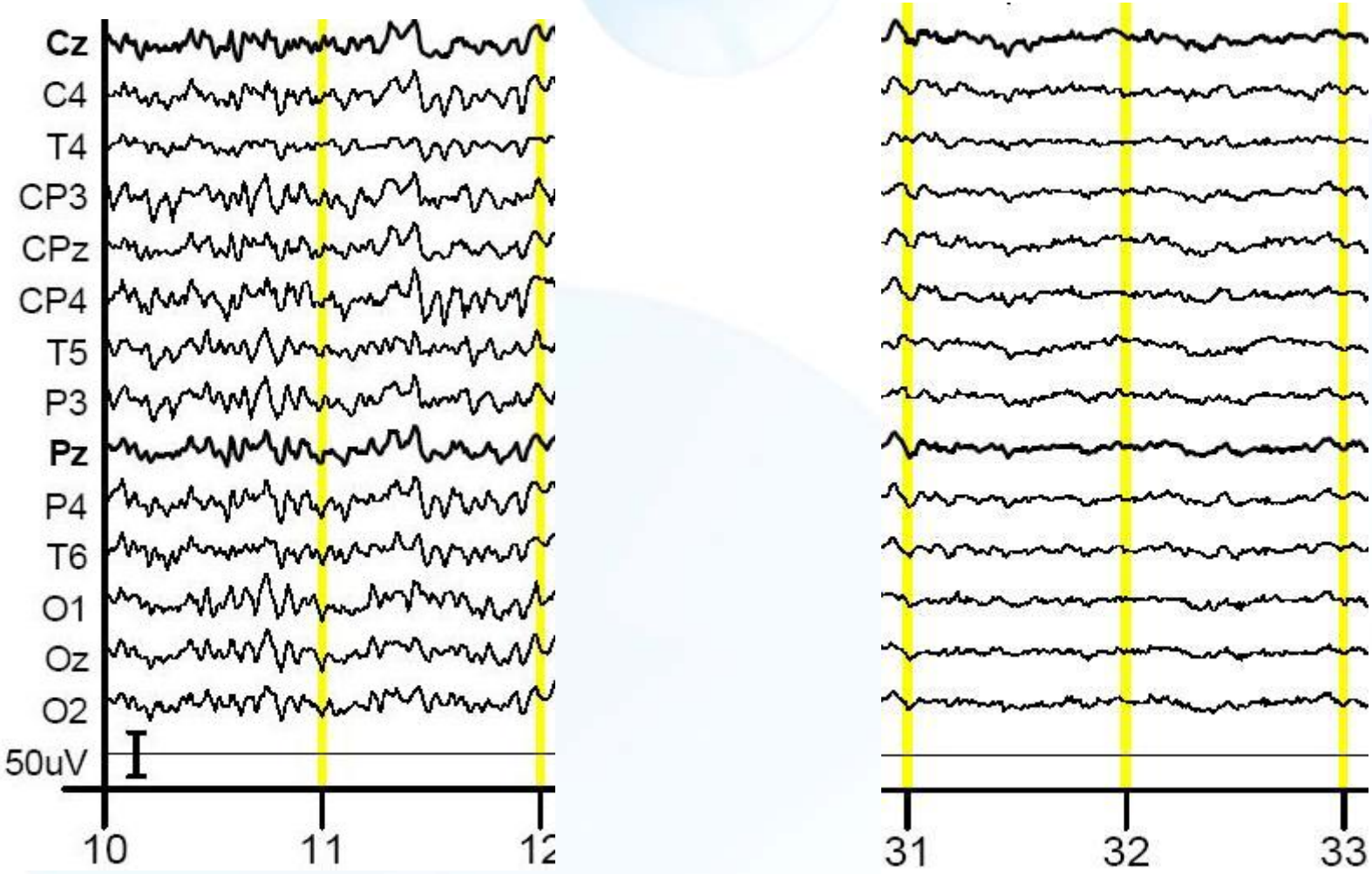
TBI post-treatment QEEG



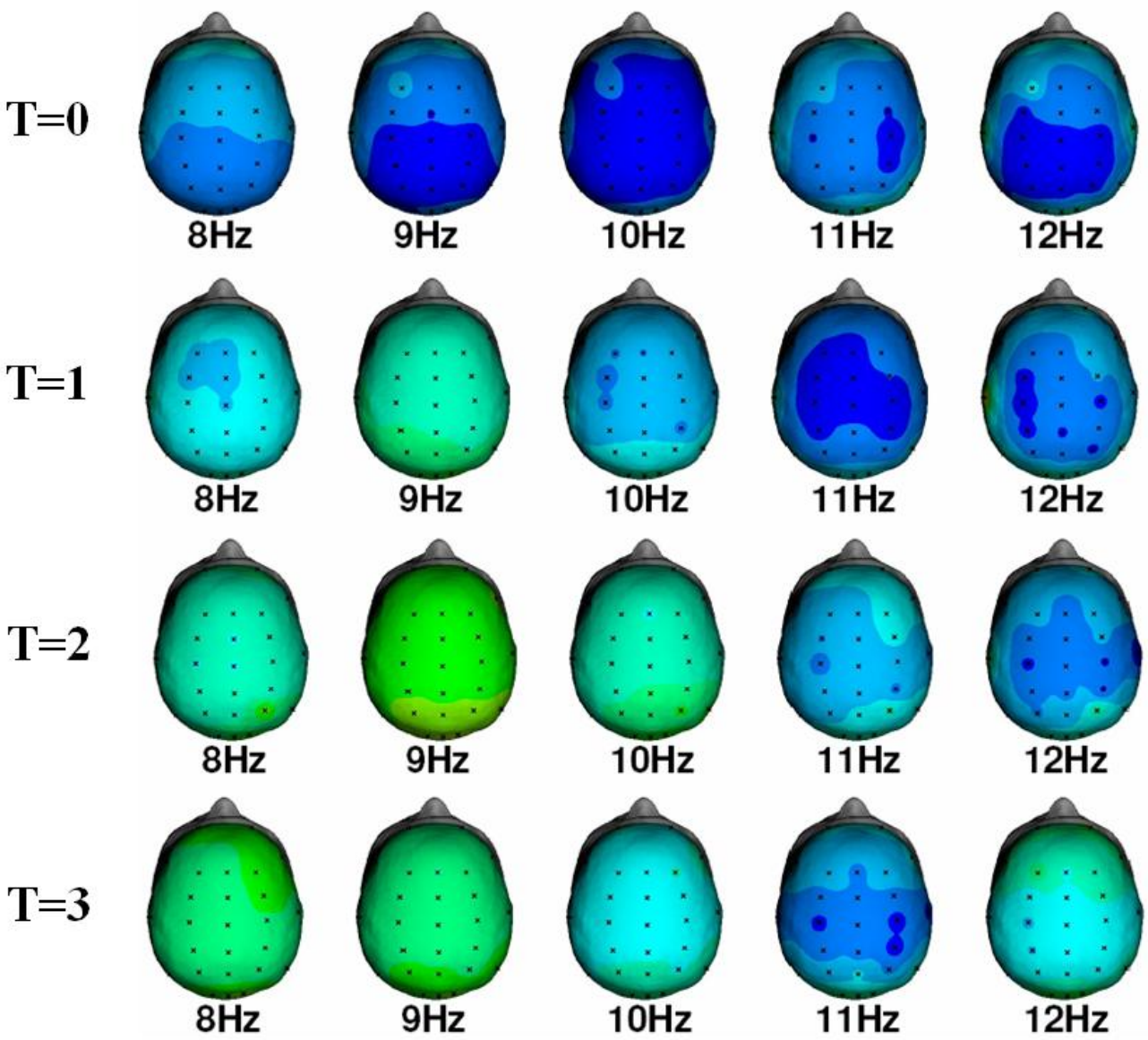




Low Voltage EEG



The effect of alcohol intake on low-voltage EEG



- Thanks for your attention!

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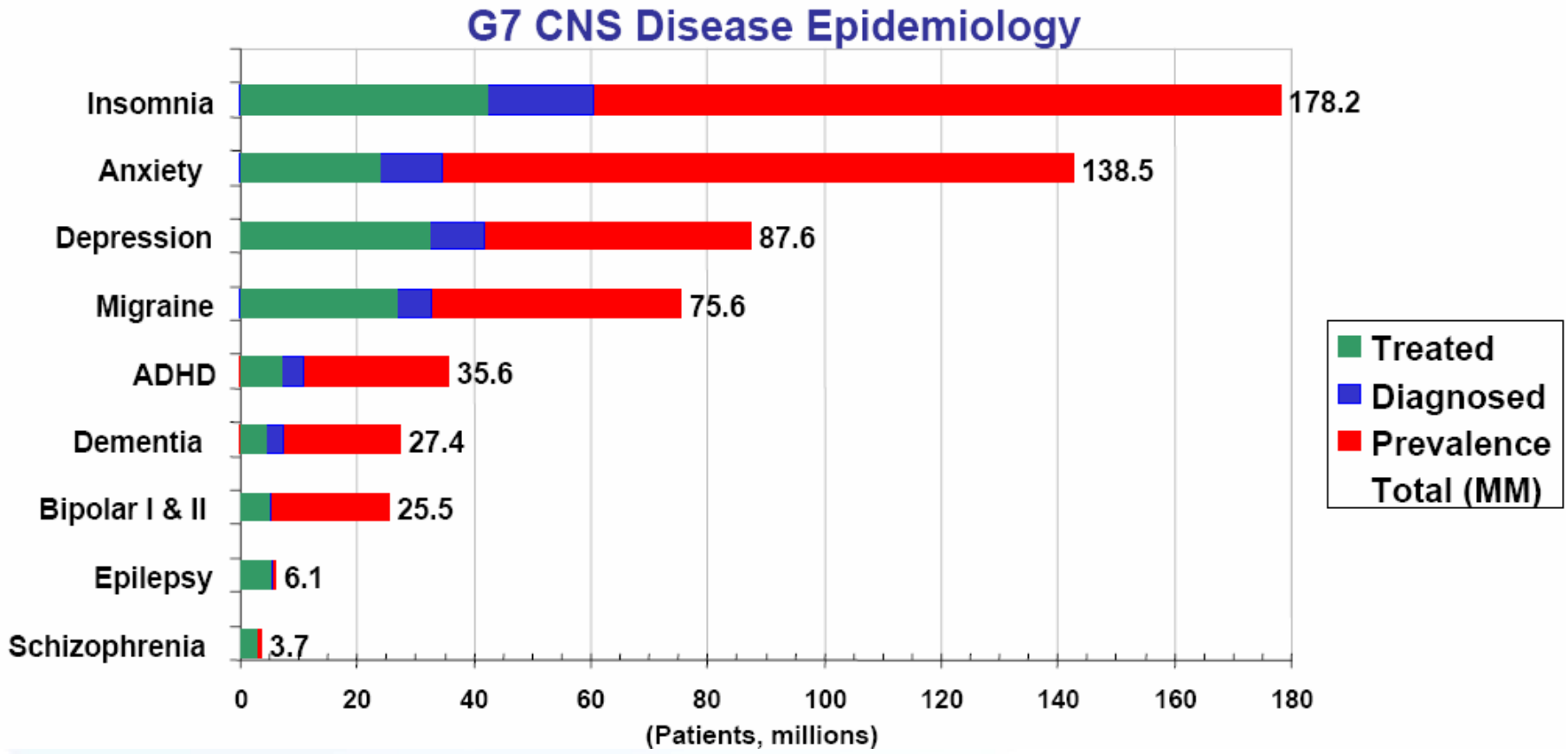
Informatief: www.personalized-medicine.eu

Significant unmet medical need in CNS disorders

- 1 in 5 people suffer from a CNS disorder
- ¼ health services patients have CNS disorder
- Economic costs exceed $400 B per year



Source: Pim Drinkenburg: Johnson & Johnson

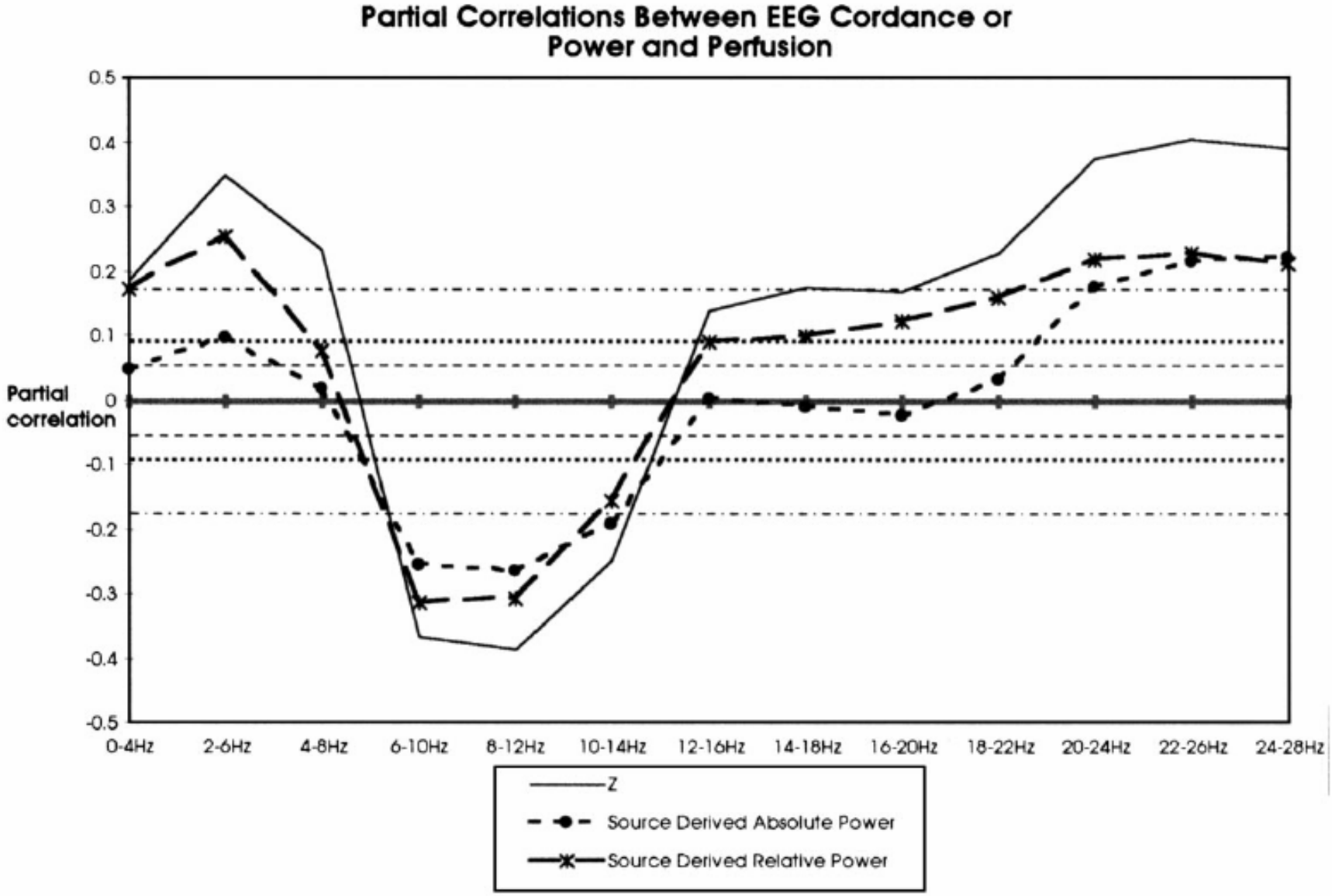


Fig. 4. Plot showing the partial correlation coefficient between EEG power and cordance values $Z_{(s,f)}$, and relative perfusion as a function of frequency band. Statistical significance is indicated by horizontal lines representing the magnitude at which a correlation coefficient attains significance: dashed line (- - - -) for P 0.05; dotted line (· · ·) for P 0.01; dotted–dashed line (– · –) for P 0.001.