ATTENTION DISORDERS

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CLINICAL NEUROPHYSIOLOGY: ATTENTION DISORDERS

- Attention Deficit: Spectral analysis of Electro-encephalo-gram is an aid in diagnosis (theta:beta-1 ratio, beta-1 power). Cogntive evoked potentials can be used to predict what medicine will work best

- Mild Cognitive Impairment: Spectral analysis of Electro-encephalo-gram is an aid in diagnosis (theta:alpha ratio), as are cognitive evoked potential latencies

ATTENTION DEFICIT/ ADD/ ADHD (A BRAIN DYSFUNCTION)

- The syndrome characterized by inattention, with or without hyperactivity and impulsivity, has had many names through the years:
  - Minimal brain syndrome
  - Hyperkinetic disorder
  - Attention deficit disorder
  - Attention deficit/hyperactivity disorder

CHARACTERISTICS

- It is a brain disorder
- It is familial
- It is common
- It affects educational, occupational and social function, and quality of life
- It is treatable
- It starts in childhood, with first symptoms invariably present by age 12
- Hyperactivity and impulsivity may or may not be present
- Although hyperactivity may improve in adulthood, inattention is a lifelong issue

DIAGNOSIS OF ATTENTION DEFICIT

- At least 6 of the following 9 symptoms:
  - Failure to give close attention to details
  - Difficulty sustaining attention in tasks/ play
  - Not seeming to listen when spoken to
  - Fail to finish work or duties
  - Difficulty organizing tasks and activities
  - Losing things necessary for tasks or activities
  - Easily distracted by extraneous stimuli
  - Forgetful in daily activities

HYPERACTIVITY/IMPULSIVITY

At least 6 of the following 9 symptoms

o Fidgeting with hands or feet or squirming in seat

o Leaving seat in situations where remaining seated expected

o Running about or climbing excessively/ subjective restlessness

o Difficulty playing or engaging in leisure activities quietly

o Being often "on the go", "as if driven by a motor"

o Talking excessively

o Blurting out answers before questions completed

o Difficulty awaiting turn

o Interrupting or intruding on others

TESTING FOR DIAGNOSIS

- The diagnosis is based on symptoms being present since before age 12

- Digital analysis of EEG (electro-encephalo-gram) aids in the diagnosis of attention deficit

- Neuropsychological testing does not determine presence of attention deficit
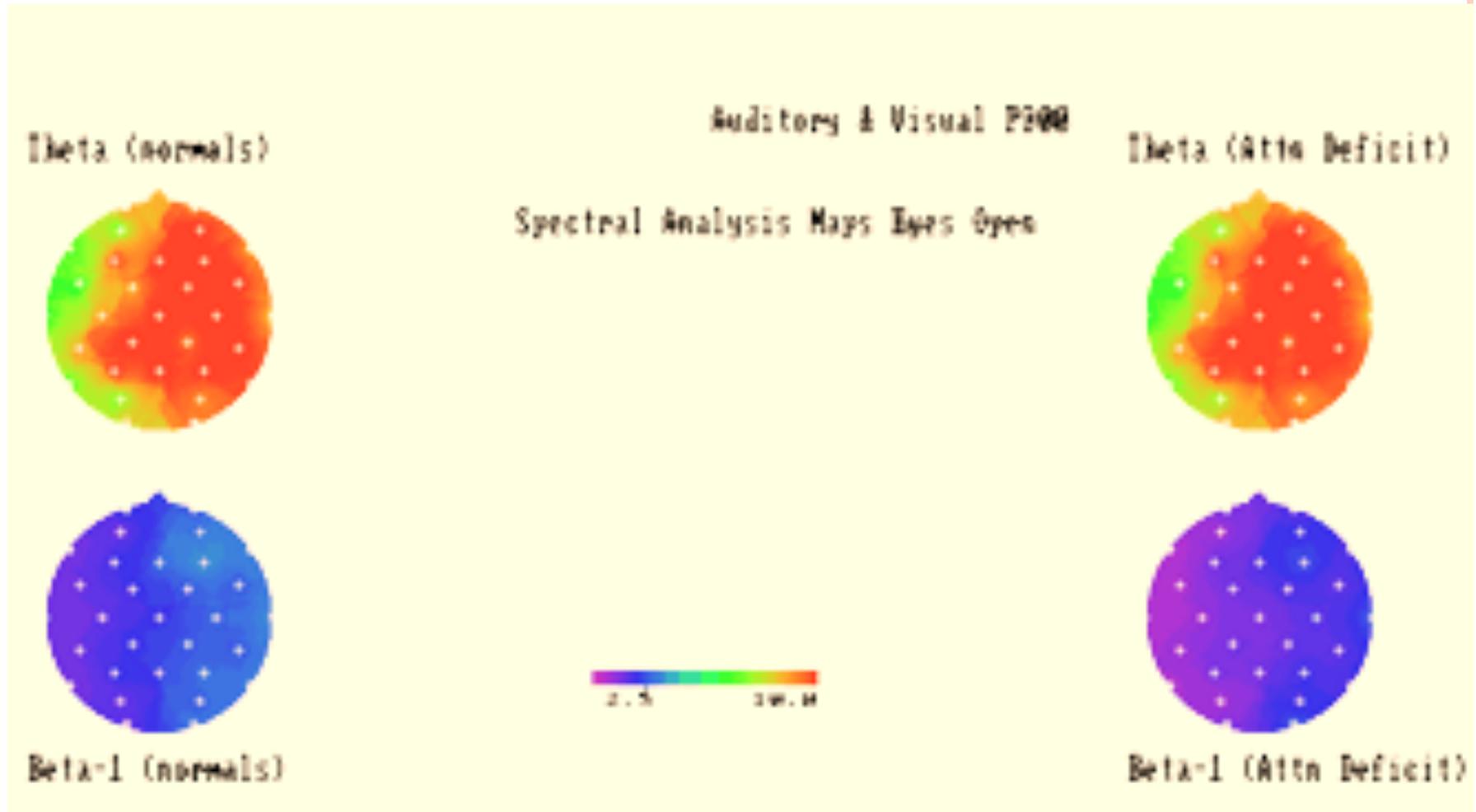
EEG DIGITAL ANALYSIS

- The EEG has different frequency bands (including theta 4-8 Hz, beta-1 13-21 Hz)

- Beta-1 activity is associated with attention, theta with drowsiness

- Theta:beta-1 ratio (tbr) has been approved by the FDA as a diagnostic aid for ADHD in children. Left fronto-central (F7, FC5) tbr >1.92 in the presence of symptoms is indicative of attention deficit in children. Tbr decreases significantly with age

- Beta-1 power during tasks of selective attention may be a better indicator, and is not related to age. Left fronto-central (F7, FC5, which is speech or Broca's area) beta-1 power <3.65 in the presence of symptoms confirms attention deficit (Sangal & Sangal, Clin EEG Neurosci 2014)

THETA & BETA-1 IN ATTENTION DEFICIT

Theta (normals)

Theta (Attn Deficit)

Auditory & Visual P300

Spectral Analysis Maps Eyes Open

Beta-1 (normals)

Beta-1 (Attn Deficit)

TREATMENT

- The best treatment is with medicines
- Medicines shown to be effective include
  - Stimulants (methylphenidate and amphetamines) which inhibit re-uptake of norepinephrine and dopamine. High dose and immediate release amphetamines release dopamine (making them more addictive)
  - Norepinephrine re-uptake inhibitors such as atomoxetine
  - Imipramine which inhibits norepinephrine (and serotonin) re-uptake and increases dopamine release by blocking alpha 1 norepinephrine receptors
  - Medicines such as guanfacine which stimulant norepinephrine (alpha 2a) activity in the brain
  - Medicines such as bupropion which inhibit re-uptake of norepinephrine and dopamine

TREATMENT DECISIONS

- Clinically, one can choose a medicine. If it works, one can continue it

- If it works partially, one can accept limited improvement or go on to the next medicine

- If it does not work, one can give up or go on to the next medicine

- Decisions about effectiveness can be global and subjective, or they can be rating scale based

- Alternatively, one can choose a medicine based on tests showing which medicine is most likely to work for a given patient

RATING SCALE

- The Attention Deficit Rating Scale is composed of 18 symptom items (9 for inattention and 9 for hyperactivity)
- Each is rated from 0 to 3 in order of severity
- This yields a 27 point inattention scale and a 27 point hyperactivity scale, for a total of 54 points

HOW MUCH IMPROVEMENT IS ENOUGH

- Pharmaceutical companies use a 25% improvement in the Attention Deficit Rating Scale as an endpoint.

- We have shown that less than 10% of patients on placebo or ineffective medicine show >50% decrease, less than 5% show a 60% decrease (Psychopharmacology Bulletin, 37:50-58, 2003).

- A 50-60% decrease in this rating scale normalizes the rating scale

OBJECTIVE METHOD OF PREDICTING RESPONSE

- Cognitive auditory and visual evoked potentials with digital analysis are an aid in predicting treatment response
- Evoked potentials are electrical responses to any stimuli, generated in different parts of the nervous system
- Cognitive evoked potentials are generated in the brain in response to cognitive stimuli or tasks

P300 ADMINISTRATION

o Subjects are given two stimuli, one less frequent than the other, occurring pseudo-randomly (the odd-ball paradigm)

o Visual stimuli may be the letters "H" and "S". Auditory stimuli may be 2000 Hz "beeps" and 1000 Hz "boops"

o Patients are asked to focus on the less frequent stimulus and indicate they have noticed it (such as by means of a button press)

P300 WAVE

- The P300 is a positive waveform occurring about 300-450 msec after the stimulus
- It occurs only in response to the less frequent "oddball" stimulus, not the more frequent stimulus
- Its amplitude is decreased when the patient is less attentive or vigilant
- Its latency is prolonged with cognitive brain disorders such as dementia and metabolic encephalopathies
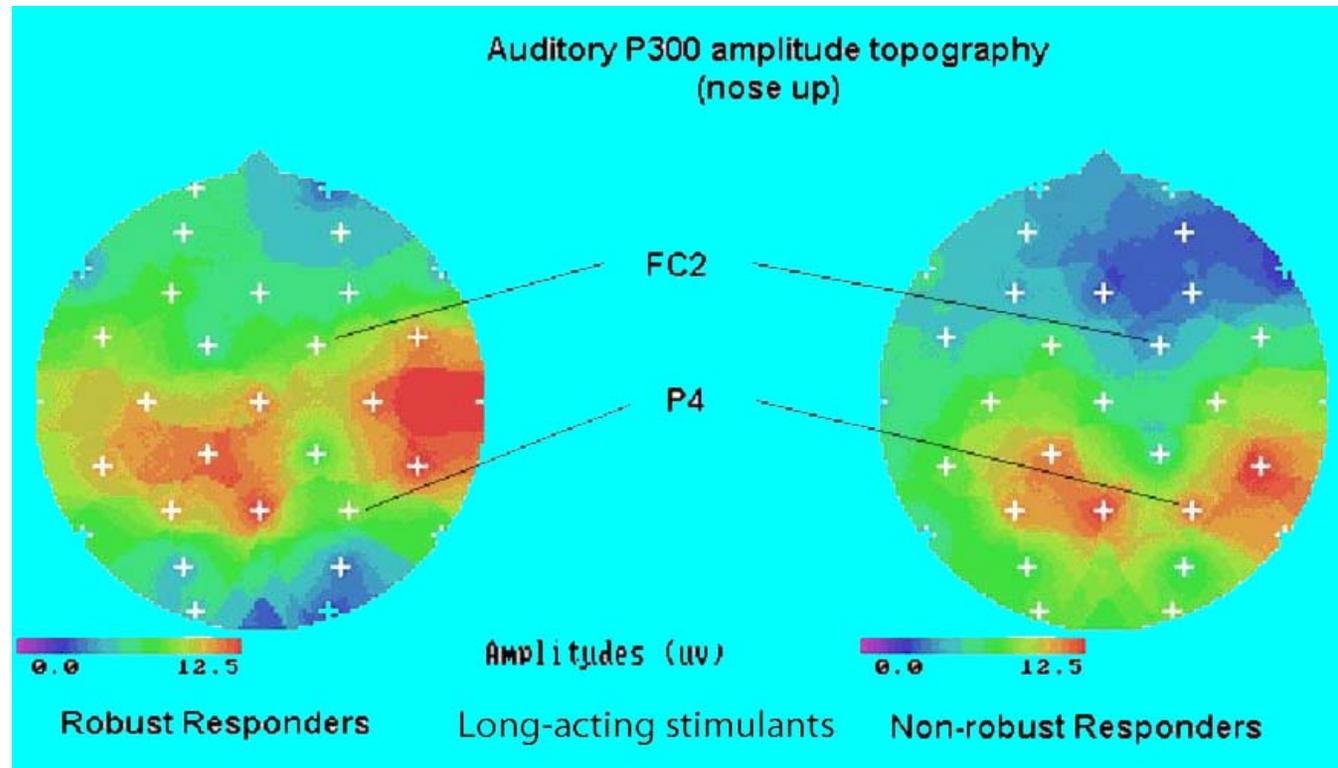
P300 AND RESPONSE TO STIMULANTS

- Patients with larger fronto-central to parietal auditory amplitude ratio (>0.5) respond robustly to methylphenidate, others do not (response rate 0.45, positive predictive value 0.67, negative predictive value 0.73) – Sangal & Sangal, Clin Neurophysiology; 115:188-193, 2004

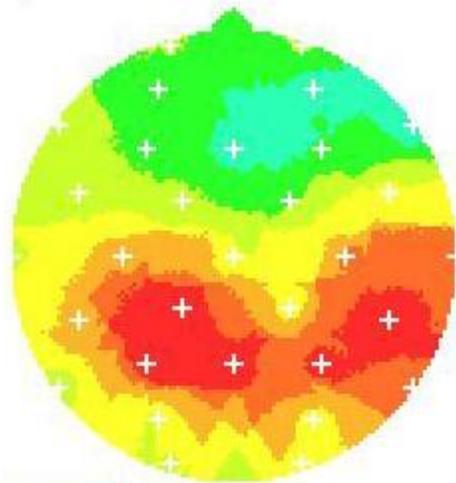# AUDITORY P300 AMPLITUDE TOPOGRAPHY AND METHYLPHENIDATE

P300 AND RESPONSE TO ATOMOXETINE

- Patients with larger 31-electrode mean auditory P300 amplitude (>6.8 μv) respond robustly to atomoxetine, others do not (response rate 0.59, positive predictive value 0.88, negative predictive value 0.67) – Sangal & Sangal, Clin Neurophysiology, 116:640-647, 2005
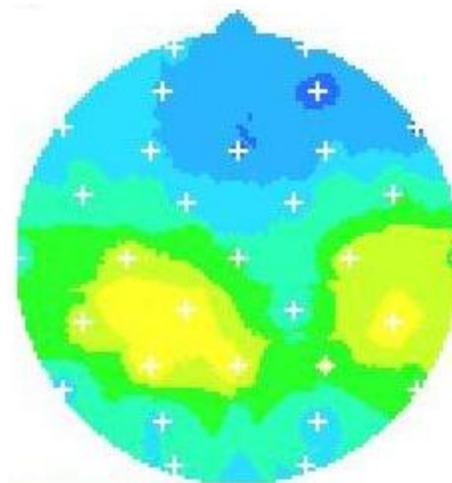
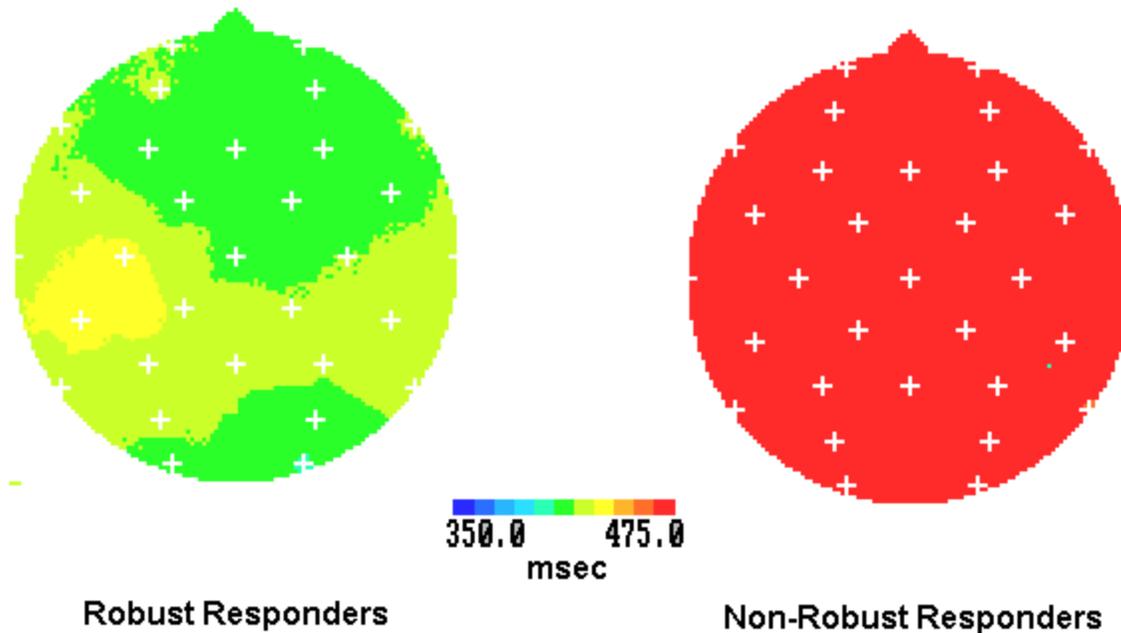# AUDITORY P300 AMPLITUDE TOPOGRAPHY AND ATOMOXETINE

P300 AND RESPONSE TO IMIPRAMINE

○ Patients with shorter 31-electrode age-adjusted mean visual P300 latency (within 0.5 SE of regression from normal mean) respond robustly to imipramine, others do not (response rate 0.41, positive predictive value 0.75, negative predictive value 0.89) – Sangal et al, Clin EEG, 26:204-213, 1995; 29:1-6, 1998

VISUAL P300 LATENCY AND IMIPRAMINE

Visual P300 latency topography (nose up)

Robust Responders

Non-Robust Responders

350.0   475.0
msec

TREATMENT PROTOCOL BASED ON P300 TOPOGRAPHY

- If right fronto-central auditory P300 amplitude (AAFC2:P4) ratio >0.5 and 31-electrode mean auditory P300 amplitude >6.8 μv, use long-acting methylphenidate or atomoxetine
- If AAFC2:P4 >0.5 and 31-electrode mean AA <6.8 μv, use long-acting ethylphenidate
- If AAFC2:P4 <0.5 and 31-electrode mean AA >6.8 μv, use atomoxetine
- If AAFC2:P4 <0.5 and 31-electrode mean AA <6.8 μv, check 31-electrode age-adjusted mean VL. If this is less than 0.5 SE from regression of normal mean, use imipramine

CONCLUSION

- Spectral analysis of EEG during tasks of selective attention is useful to confirm attention deficit (ADD/ADHD) in patients with symptoms of attention deficit

- Topographic mapping of Evoked Potentials during tasks of selective attention is useful to predict which medicine will work best for a give patient

MILD COGNITIVE IMPAIRMENT

- Mild Cognitive Impairment (MCI) is characterized by the symptom of worsened memory without change in other cognitive functions such as planning, object recognition, language

- In dementia, memory impairment exists along with other changes in cognitive function

QUESTIONS IN MCI

○ Question 1: Is there really a significant objective memory impairment or is this within normal limits?

○ Question 2: Is there a cause (hopefully reversible) for memory impairment

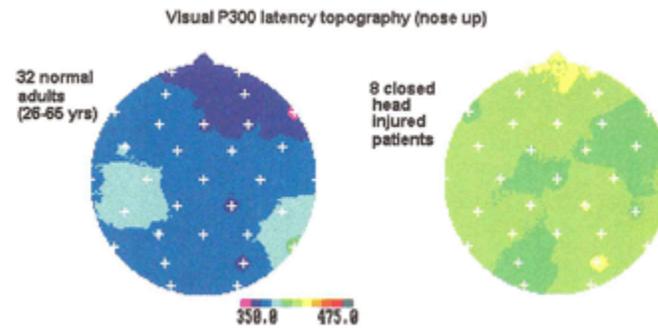○ Question 3: What is the current baseline cognitive functioning?

Q 1: IS THERE A SIGNIFICANT IMPAIRMENT?

- If all of the following are normal:
  - Background frequency of EEG
  - Theta-alpha ratio (digital analysis of EEG)
  - Auditory and visual cognitive EP latencies (within 1 SE of regression from normal mean
  - Working memory on neuropsychological testing and discrepancy with verbal comprehension
  - Auditory memory on neuropsychological testing and discrepancy with predicted auditory memory

  then there is no significant impairment at present

VISUAL P300 AND MCI (DUE TO CLOSED HEAD INJURY)

Visual P300 latency topography (nose up)

32 normal adults (26-65 yrs)

8 closed head injured patients

350.0   475.0

Q 2: IS THERE A CAUSE?

- MRI for space occupying lesions in the brain, old strokes, or white matter changes indicative of vascular insults (inadequately controlled diabetes or high blood pressure)

- Blood work for B12, folate, thyroid functions, metabolic changes, anemia, high lipids, high hsCRP (indicative of generalized inflammation)

- Apo-lipoprotein E testing for genetic predisposition to lipid disorders and to Alzheimer's

- Polysomnography for sleep apnea

Q 3: CURRENT BASELINE?

- Baseline can be established for comparison with future tests to determine worsening:
  - The background rhythm of the EEG
  - The theta-alpha ratio from the digital analysis of the EEG
  - Auditory and visual cognitive EP latencies
  - Verbal comprehension and working memory on neuropsychological testing
  - Auditory memory on neuropsychological testing

MEDICINES FOR MCI

- Patients complaining of memory impairment often are prescribed acetylcholinesterase inhibitors (like donepezil)
- These slow down the worsening in Alzheimer's
- Not only do they not have an effect on non-demented patients, they actually increase the death rate in these patients
- Should definitely not be used if memory impairment not clearly objectively established