P1- Plenary Session
The Donald Altman, MD Lectureship
Functional Imaging in Pediatric Neuroimaging

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Disclosure of Relevant Relationship

- Dr. Altman (or spouse/partner) has not had (in the past 12 months) any conflicts of interest to resolve or relevant financial relationship with the manufacturers of products or services that will be discussed in this CME activity or in his presentation.

- Dr. Altman will support this presentation and clinical recommendations with the “best available evidence” from medical literature.

- Dr. Altman does not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.
Acknowledgement

• Byron Bernal, M.D
FUNCTIONAL MRI

• fMRI uses the paramagnetic effects of deoxyhemoglobin to provide endogenous contrast to map cortical brain activation
• The region performing the task has increased blood supply
• fMRI investigates brain functions: motor, visual language, cognitive functions, etc.
• fMRI has an important role in surgical planning and evaluation of cognitive functions
TP, Epoch, Cycle, and Paradigm

TASK = PARADIGM
Definitions and time

- Time Point 14 slices through the brain 2 sec
- 10-15 TP per Epoch
- Epoch 20-30 sec
- Paradigm is at least 10 Epoch or 5 cycles
- 100-150 TP per series 200-300 sec
- 1400-2100 slices through the brain
- 3-5 minutes per Paradigm
Methods

• Task oriented
• Sedated
• New methods
  – Resting state fMR  rs fMR
  – Pharm fMR
Task oriented f MR

- Motor
- Auditory
- Language
- Visual
- Memory
- Executive functions
  - Motor and cognitive inhibition
Localization of functions

Brodmann’s areas

• 50 areas
• Different from anatomic boundaries
• Deep cortex not included
The paradigm toolbox
Motor and sensory

- **Squeeze sponge**
- **Tapping fingers (each hand separately).** Condition: tapping each finger tip with the thumb. Control: Rest
- **Tapping fingers (alternating hands).** Condition: as in the previous. Control: tapping fingers of the other hand, while keeping at rest the first hand in movement.
- **Tapping fingers both hands.** Condition: both hands tapping all fingers simultaneously. Control: rest (for subjects with poor pre-test performance the previous tasks.)
- **Making a fist.** Condition: patient make a tight fist. Control: rest. For patients not capable to do previous tasks.
- **Ba-da-ga.** Condition: saying silently BAH-DAH-GA. Control: rest (motor activation of the face)
- **Moving the toes.** Condition: fanning toes. Control: Rest. (we have not try variations on this task)
- **Rubbing:** Condition: Rubbing a hand. Control: rest. No stimulus
Motor Activation

Paradigm: motor
Task: squeeze sponge
Off: Rest
Activation: Pre and postcentral contralateral cortex
Clinical applications: Motor mapping
Brain Reorganization
MotorTransference

15 year old patient
Intractable epilepsy since he was 12
Left apraxia and mild paresis
Paradigm:
Left hand finger tapping
Language Mapping
Auditory

• Mother voice. (MV). Condition: a pre-recorded speech from the mother is played back to the child. Control: Rest. Movie presentation language of characters in Ice Age movie vs rest of natural sounds
Language

Listening to a Story. (LTS): Control: “thinking of a blue sky” or just rest 90%

Listening to a story II. Control: same text played backwards. 70%

Antonyms. Condition: thinking of words that mean the opposite. Control: as in LTS

Auditory Description Task. (ADT). Condition: Patient presses a button if a description matches a word. Control: Patient presses a button when a tone is presented,

Auditory Category Task. (ACT). Condition: Patient presses a button when hearing a word that matches a given category. Control: pressing a button when hearing a tone

Movie presentation with and without language
Different Rest Epochs
Paradigm: Antonym Production
Task: Subject thinks antonyms when prompted
Off: “Thinking of a blue sky”
Activation: Left Brodmann’s 44-45, Broca’s area
Left Brodmann’s 21-22, aka as Wernicke’s area
Language Mapping

BEST RESULTS WHEN USE GROUPS OF TASKS

- Listening To A Story
- Antonym Production
- Auditory Processing
- Movie
Language Mapping
Targetting Receptive and Expressive Areas

LTS

Antonym

AP
9-year-old left handed patient with intractable seizures. **MRI** diffuse left cerebral cortical dysplasia. **fMRI:** Demonstrated right auditory and language (receptive and expressive dominance) 
Patient underwent left hemispherectomy. Transient post-op mutism but eventual recovery without language impairment.
Language Dissociation

Antonyms
Listening to a story
Antonym production
Visual

- **Flashing Lights. (FL).** Condition: flashes of red light presented by means of special goggles placed in front of the eyes. (Usually the eyes are closed). Control: lights off.

- **Whirling circles.** Condition: Black and white stripped concentric circles are displayed on a screen. Control: sight fixed in a cross.
10 year old with seizures
MRI
• Right posterior parietal and occipital lobe cortical dysplasia
• Right subependymal gray matter heterotopia
fMRI
• There is only activation of the left visual cortex with visual task
• Important for surgical planning and counseling.
Patient underwent right occipital lobectomy.
Memory

• **Visual discrimination task.** Condition: subject presses a button if the scene presented corresponds to indoors. Control: Subject presses a button when a vertical line placed on top of a colored abstract background is shifted to the left. The background is made out of the same photos utilized for the condition.

• **Memory navigational task.** Condition: subject recalls silently the geographical and reference landmarks when mentally navigate between familiar points (for example: between the house and the park). Control: “think of your breathing.”
Memory activation

- Paradigm:
  - Visual discrimination
    indoors vs. outdoors
  - Visual navigational tasks
    for example: mentally walking the neighborhood
Navigational task

Activation is predominant in the left parahippocampal area

*Sensibilidad: >90% (Jokeit et al, Neurology, 57. 2001)*
Reduced activation of the mesiotemporal region ipsilateral to the epileptogenic region correlates with a favorable memory outcome after right-sided [anterior temporal resection]
Executive function

• **Motor Inhibition Task. (MIT).** (also known as go no go task). Condition: A distinct letter is displayed on a screen every second. Patient should NOT press a button when letter X is presented. Control: an epoch with no Xs on it.

• **Color Stroop Task. (CST).** Cognitive inhibition Condition: Names of colors are presented with a different color font. For example: **RED.** Subject has to mentally name the font color, not what the word says. Control-1: Same instruction, but this time the words match the color they name. For example **RED.** Control-2: Sight fixed in a cross.
Inhibition

Motor vs. Cognitive Inhibition
Motor inhibition
Task: Go / No-Go
N=24 subjects, 12 Males
Cognitive Inhibition
Task: Color Stroop
fMR in sedated subjects!

- Auditory
  - Listening
    - Story
    - Mother’s voice
- Visual
  - Flashing lights
- Somatosensory
  - Rubbing and extending the hand
fMRI under sedation

- Passive paradigms
- Low Z scores expected
- Visual activation obtained subtracting off from the on Negative BOLD
- Auditory activation predominates in primary and receptive language cortex and is usually lateralized.
- Some cases show activation of Broca’s area
Brain Activation in Sedated Children: Auditory and Visual Functional MR Imaging

PUBLISHER: To map developing areas of activation with functional magnetic resonance (MR) imaging in sedated children by using passive auditory and visual tasks.

MATERIALS AND METHODS: Forty children between 2 months and 9 years old were examined and grouped according to age. Children were selected from patients referred to undergo brain MR imaging. Patients received pentobarbital (3.0–7.0 mg per kilogram of body weight) or chloral hydrate (50–75 mg/kg). The functional MR imaging study was performed at the end of the examination. Paradigms consisted of flashing lights at 8 Hz displayed on special goggles and a prerecorded mother’s voice presented through headphones. Activation maps were obtained from a paired t test with a P value of .0005 (uncorrected).

RESULTS: The visual stimulus produced statistically significant negative values in the rostral aspect of the primary visual area (28 [90%] of 31 patients). The auditory paradigm activated either temporal or frontal areas in 26 (68%) of 31 patients. There was more frontal activation in the older children.

CONCLUSION: Visual and auditory cortices can be activated in children who have been sedated. Visual responses show negative values in the rostral visual cortex, independent of age. Auditory activation is seen in temporal and frontal lobes.
Modern sedation

• Anesthesiologist administered
• Many new drugs administered and potential for combinations to improve percentage of patients with activation
Sedation scheme

Precedex <1 microgram / kg
auditory and motor

rsfMRI

Propofol <100 micrograms / kg
visual
Sedated Children Results of IV Propofol and Precedex combination

- Auditory with Precedex 90% activation
- Visual with Propofol 90% activation
Motor
Passive movement of right hand
Passive Paradigms

Visual (Flashing Lights)

Auditory (Listen To Story)

7-y-o-right handed girl.
A 6 yr old boy hearing Mother’s voice

See expected activation of receptive language area as well as expressive language region
New Methods

• Resting state fMRI (rs fMRI)
  – independent component analysis (ICA)
  – Regional Homogeneity of BOLD signal (ReHo)
  – Amplitude Low Frequency Fluctuations
    • ALFF
    • FALFF (Fractional-ALFF \rightarrow Normalized)

• Pharmacology-fMRI (ph-fMRI)
• EEG triggered-fMRI
• Fetal rs fMRI
Rs fMRI

Independent Component Analysis

Postprocessing method

• The brain is searched voxel by voxel (spatial correlation) to determine similar time line graphs for a series of time points (200 TPs 6 minutes 40 sec) fast Fourier transform determines similar group locations and these are co registered on EPI images
rs fMRI

• It depends on spontaneous cortical activity
• NO paradigm needed
• Several components
  – Temporal or spatial correlation
• Observable even under sedation
• Reveal connectivity
• Shows other physiological cyclic events
Methods

• 200 TP sequence  6 minutes 40 sec
• TR 2 sec
• Software automatically samples 20-40 components
• Found functions at certain frequencies
  • Neural rhythms .01Hz to .1 Hz
rs fMRI

- Spontaneous brain activation
  - Very Slow Cerebral rhythms (< 0.1 Hz)
  - Usually with symmetrical bihemispheric distribution
  - Conectivity
Neuronal component: Primary visual area
ICA: Neural Networks

ICA
Component extraction validation

Standard analysis
Task: Listening to a Story

ICA
resting state
Does an hemimegalencephalic hemisphere have motor representation?

Possible Clinical applications
Independent Component Analysis  Motor Component
Default Mode Network

Network active when the individual is not focused on the outside world and the brain is at wakeful rest
Default Mode

Posterior Default Mode
Post Cingulate – Precuneus – TOP

- Monitoring
- Consciousness
Deactivates with cognitive workload

Anterior Default Mode
Ant Cingulate – Mesial – Prefrontal

- Attention
- Executive
PDM
DM COUNTER-CORRELATION normal volunteer

GLM (OLS) on time series

<table>
<thead>
<tr>
<th>GLM β's</th>
<th>F-test on full model fit</th>
<th>Contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE(1): -0.83</td>
<td>PE(2): 1.36</td>
<td>F = 17.20, dof1 = 2, dof2 = 147, p &lt; 0.00000 (uncorrected for #comp.)</td>
</tr>
</tbody>
</table>
Task Related DM
Psychiatric Patient

GLM (OLS) on time series

<table>
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<tr>
<th>GLM β's</th>
<th>F-test on full model fit</th>
<th>Contrasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE(1): -0.07</td>
<td>F = 1.44, df1 = 2, df2 = 147, p &lt; 0.24059 (uncorrected for # Comp.)</td>
<td>COPE(1): z = -0.39; p &lt; 0.65313</td>
</tr>
</tbody>
</table>
Dissociated default mode
18-y-o-b with auditory and visual hallucinations
CONDITIONS IN WHICH DM DOES NOT DE-ACTIVATE IN PRESENCE OF COGNITIVE LOAD

- **ADHD**

- **BIPOLAR DISORDER**

- **SCHIZOPHRENIA**

- **AUTISM**

These conditions seem to produce poor or no deactivation of the default mode coupled with cognitive load (for instance associated to fluency tasks, working memory, executive control, etc).
Normative data

• RS-fMRI
  – 1000 normal subjects repository
  – Public released
  – Multisite effort
Source rs-fMR Normal subjects

- Data from a large sample RS-fMRI dataset publicly released as "The ADHD-200 Sample" in the "1000 Functional Connectomes Project."

- **Children** ADHD-200 Sample.
Rs fMR connectivity
ROI-based Functional Connectivity
BA22 (Wernicke’s)
ROI-based Functional Connectivity
BA44 (Broca’s)
Possible applications of ph-fMRI

- Drug development
  - Analgesics
  - Anesthetics
- Follow-up of:
  - Psychiatric disorders
  - Abnormal movements
  - Control of drug-addiction
PHARMACOLOGY & rs-fMRI
fMRI in epilepsy focus detection

- Ictal fMRI
- Interictal fMRI (EEG-fMRI)
Ictal fMRI

• Accidental (seizure happens in the magnet)
  – Should be subtle
• But may be anticipated
  – Reflex epilepsy (provoked)
• Non-motor seizures
Interictal fMRI

- EEG-fMRI
  - Timepoints manually triggered by discharges
  - Continuous acquisition with registered discharges

- Requirements:
  - Frequent discharges
  - Cooperative patient
  - MR compatible EEG equipment
EEG-fMRI
(triggered by discharges)

Karsten Krakow
Rs-fMRI and fetal fMRI
Fetal rs-fMRI
22 week Fetal rs-fMRI
• Pediatric fMR is looking into the minds of our future