fMRI in pediatric epilepsy

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Disclosures

- no relevant financial disclosures
- some of the analysis techniques discussed are not FDA approved
Goals

1. Understand task based functional MRI including preoperative motor and language localization in application to pediatric epilepsy.
2. Review current work with resting state fMRI and implications for potential future clinical applications in epilepsy.
Outline

- A. Goals of clinical fMRI in pediatric epilepsy
- B. Review basics of fMRI
- C. Challenges of fMRI in children
- D. Sensorimotor fMRI (task based: active and passive)
- E. Language fMRI (task based)
- F. Memory fMRI (task based)
- G. Resting state fMRI: potential/ future applications
A. Goals of clinical fMRI in pediatric epilepsy:

Map eloquent cortex:
  Sensorimotor
  Visual cortex

Proximity to planned lesion resection.
Detect displacement/transfer of function.
A. Goals of clinical fMRI in pediatric epilepsy:

Language location/ lateralization:
- predicting post surgical deficits
- obviating need for grid
[second surgery]
A. Future goals of clinical fMRI in pediatric epilepsy:

- Memory; hippocampal activation
- Seizure focus mapping
B. Review basics of fMRI

- Physiologic basis: BOLD (blood oxygen level detection) effect
- Task based paradigm (Block/Box car design)
- Data processing
Feed forward control: regional cerebral blood flow

After Attwell et al
Nature 2010
Feed forward control: regional cerebral blood flow

After Attwell et al. Nature 2010
Neurovascular coupling

Baseline

Neuronal Activation
[functional hyperemia]

Dependent on an intact neurovascular reserve:
Neurovascular coupling

Baseline

Neuronal Activation
[functional hyperemia]

Dependent on an intact neurovascular reserve:

Potentially compromised:
- AVM
- Tumor (shunting/hyperemia)
- Active epileptic focus

[Restricted flow - adults]
**BOLD signal**

Deoxyhemoglobin (diamagnetic) → Oxyhemoglobin (paramagnetic)

Less dephasing ➔ ↑signal

$T_2^*$ signal $\Delta$ between each voxel at baseline and activated state.
Deoxyhemoglobin (diamagnetic)  Oxyhemoglobin (paramagnetic)

Detection $T_2^*$ $\Delta$ potentially compromised by Motion between baseline and task (change SI in voxel due to different contents)
Deoxyhemoglobin (diamagnetic) \rightarrow Oxyhemoglobin (paramagnetic) \rightarrow T2* \\

Detection T2* Δ potentially compromised by local susceptibility artifact- e.g. metal (braces, shunt), bone (skull base)
fMRI BOLD signal change associated with neuronal activation

1. *Increased CBF* that exceeds increase O2 extraction resulting in *increased oxyhemoglobin*
2. Deoxyheme (diamagnetic) ➔ oxyheme (paramagnetic) ➔ *decreased susceptibility detected as change (↑) T2*
3. *Indirect measure of neuronal activity:* vascular changes mediated by astrocytes/(neurons)
4. *Temporal delay* in vascular response of a few seconds
5. *Spatial resolution limits* dependent on imaging parameters
6. *Signal change is small,* 3%-5%
fMRI: Block (Boxcar) design - Task (activated state) versus baseline

![Graph showing voxel signal level and stimulus timecourse over time](image)
fMRI BOLD signal fluctuation sources

1. Cardiac pulsations: blood and CSF (inflow effects),
2. Breathing oscillations (changes in Bo field- chest expansion),
3. Bulk motion (including breathing),
4. Scanner instability
5. BOLD and flow fluctuations w/ slow changes in end tidal CO2
6. BOLD and flow variation from neuronal modulation secondary to task.
Data processing: task based fMRI

[Vendor vs FSL, SPM, AFNI...]

Acquisition

- BOLD data
- Bo map
- Structural MR

Preprocessing steps

- Reconstruction from k-space data
- Motion correction
- Slice timing correction
- Spatial filtering
- Temporal filtering
- Global intensity normalization:

Statistical analysis

- Correlate model at each voxel separately
- Measure residual noise variance t-statistic = model fit / noise amplitude
- Threshold t-stats and display map
Mapping eloquent cortex: clinical challenges -

- Paradigms need to be robust enough to have statistical validity in the individual patient.
- Performed on a clinical scanner (3T)
- Generally need whole brain coverage
- Post processing (commercial software, regulatory)
- Validation
Mapping eloquent cortex in children: clinical challenges-

- Tailoring tasks for age/ cognitive ability
- Choice of activation and reference tasks is critically important in children
- Motion
- Some with limited or no ability to perform active tasks
- MRI under sedation
- Brain malformations
- Real time feedback- very useful!
D. Sensorimotor fMRI in children (task based)

- Hand
- Foot
- Face (movement artifacts problematic)
- Passive tasks
Motor mapping: active task based block design - left hand (vs right hand)
E. fMRI Language mapping (task based; block design)

- Choice of task
  - word generation
  - semantic decision
E. fMRI Language mapping (task based; block design)

- Choice of task:
  - Verb generation from word or picture - depending on level of reading
  - Sentence generation [older, proficient with language]
Language lateralization:

Functional MR imaging (fMRI) using task-based paradigm:

Verb Generation task

Left dominant

Right dominant
Language lateralization: left dominant: Verb generation- mapped to 3d surface

Right

Left

= activation

= de-activation
Language lateralization index: Magnitude of change in R vs L Broca with task

Masks for Brodmann areas 44 and 45 +
strongly left dominant. Lateralization index for Broca’s areas:
Left: 0.23 Right: -0.06
Strongly RIGHT dominant (R >> L).
Laterazilation index for Broca’s areas:
Left: -0.12 Right: 0.18.
fMRI Language results compared to Wada: meta analysis, Dym et al Radiology 2011

- Twenty-three studies, comprising 442 patients.
- All block design: Most (15/23) used word generation
- fMRI for atypical (right or mixed) language dominance - compared with the Wada test:
  - Sensitivity: 83.5% (95% CI: 80.2%, 86.7%)
  - Specificity: 88.1% (95% CI: 87.0%, 89.2%)
fMRI BOLD cortical mapping; under sedation/anesthesia:

- BOLD response is seen with appropriate stimuli in sensorimotor, visual, auditory cortex.
- Response is dependent on anesthetic agent and depth of anesthesia:
fMRI cortical mapping; sensorimotor task under anesthesia-

- Block design: task state compared to baseline
- Alternating right versus left passive finger movement.
- Propofol anesthesia: ask anesthesia to ‘run light’
fMRI: Block design alternating passive finger movement under anesthesia

Passive Left and Right finger movement

Activation mapped to 3d surface
fMRI: passive *right* hand/finger movement
anesthesia:

Sensorimotor region cortex activation: adjacent a **tumor** (arrow).
fMRI BOLD cortical mapping; visual task under anesthesia-

- Block design: task state compared to non task/baseline.
- Flashing screen, on/off (6 Hz); eyes closed.
- Propofol anesthesia
fMRI: Child under propofol anesthesia:

Flashing Screen: Block design

Deactivation primary visual cortex
(Peripheral visual cortex)
Temporal lobe assessment with fMRI:

Surgical planning in TLE requires assessment of hippocampal memory function so as to avoid bilateral damage. (e.g. HM)

This is part of the Wada test (intra-carotid Na amyntal)

Clinically relevant evaluation of mesial temporal lobe memory function with fMRI has been challenging

The hippocampus is ‘always recording’
F. Memory fMRI (task based)

- Choice of task: autobiographical mental navigation through familiar territory- ‘home walk’, ‘school walk’
- Block design: alternate with counting
- Correlation with Wada memory and surgical outcomes; on going
Block paradigm: Hometown Walk task
(autobiographical: mental navigation of familiar geography)

Problems with task based fMRI in clinical evaluation of mesial temporal lobe memory function:

- Difficulty in establishing clinically efficient tasks: Weak activation
- Varying cognitive capabilities (DD, younger children)
Memory: para/hippocampal activation

L>R

R>L
Memory: para/hippocampal activation
L=R

None
Memory: autobiographical task

Current status of SCH pediatric experience:

- ‘home walk’/’school walk’ autobiographical memory paradigm is effective in children with epilepsy in activating mesial temporal lobe structures in individual patients.
- Limited number of patients studied
- Incomplete memory outcome data.
- Whether this fMRI memory paradigm is viable for estimating post surgical functioning is pending.
fMRI in the pediatric clinical world: techniques not requiring cooperation

- fMRI conducted under anesthesia. (Passive task paradigms).
- Non task approaches- resting state fMRI (rs fMRI):
  -sensorimotor.
  -early work mesial temporal lobe function
G. Resting state fMRI (rs fMRI):

- Spontaneous fluctuations in baseline
fMRI: BOLD signal fluctuation
fMRI BOLD spontaneous fluctuation

BOLD and flow fluctuations w/ spontaneous neuronal activity. (predominant freq. components < 0.1 Hz).
fMRI BOLD signal fluctuation sources:

1. Cardiac pulsations: blood and CSF (inflow effects),
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3. Bulk motion (including breathing),
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6. BOLD and flow variation from neuronal modulation secondary to task.
7. BOLD and flow fluctuations w/ spontaneous neuronal activity. (predominant freq. < 0.1 Hz)
Spontaneous variation in BOLD signal:

Variable correlation of these spontaneous BOLD fluctuations between voxels.

Functional connectivity MRI (fcMRI):
Patterns in brain regions which demonstrate synchronicity in spontaneous BOLD signal fluctuation
Resting state fMRI BOLD cortical mapping; under sedation/anesthesia:

- Persistence of spontaneous BOLD variation in sleep, sedation, anesthesia.
- Spontaneous modulation is dependant on anesthetic agent and depth of anesthesia:
Methodology: functional connectivity analysis in resting state fMRI:

- Resting state EPIBOLD sequence: Siemens 3 T.

- Subject’s dataset co-registered linearly with MNI space.

- Analysis performed using 1000 Functional Connectomes Project scripts based on AFNI and FSL software packages.

- [motion correction, regression of noise: CSF, cardiac]
Seed placed in left somatomotor cortex using MNI standard space location after alignment to standard space:

Somatomotor seed (39, -27, 51)
Functional connectivity (fc) resting state fMRI: analysis approaches

-A priori approaches: correlation with selected (seed) regions
  Seed selection based on individual anatomy or standardized after co-registration with standard space

-Data drive techniques: independent component analysis (ICA). Variable number of components depending on the data and processing constraints (some/many can be nuisance/noise) - mostly used in group analysis.
Functional connectivity resting state fMRI

Seed-based analysis performed using 1000 Functional Connectomes Project scripts based on AFNI and FSL software packages. Individual datasets coregistered **linearly** with MNI space.

SM (39, -27, 51) V1 (18, -72, 12) PCC (6, -48, 39) Ventral Precuneus (0, -62, 24) Retrosplenial (6, -54, 10)
Spaciotemporal patterns detected in spontaneous BOLD fluctuations

Spaciotemporal patterns of the synchronicity in this spontaneous BOLD fluctuations match known functional networks.
Resting state fMRI/ functional connectivity-advantages over tasked based paradigms:

- Doesn’t require patient cooperation with task performance
- Single multipurpose data set
- Persists in sleep and under anesthesia
- Potential better S/N then task based: task related modulation of BOLD is a minority of the BOLD variation.
Task fMRI versus fc MRI mapping of sensorimotor cortex

Fitted ROC curves task and rs MRI; 8 subjects: Mannfolk et al 2011
Resting state fcMRI network including primary visual cortex under propofol anesthesia

Seed-based analysis performed using 1000 Functional Connectomes Project
Hippocampal-parietal network:

Hippocampal formation correlated regions: L&R inferior parietal lobules; posterior cingulate; ventral precuneus complex; retrosplenial cortex

(Vincent 2006)
Hippocampal-parietal network: preliminary study of mesial temporal lobe

- Resting state EPIBOLD sequence: Siemens 3 T.
- Subject’s dataset were coregistered linearly with MNI space.
- Analysis was performed using 1000 Functional Connectomes Project scripts based on AFNI and FSL software packages.

**Seeds:** (MNI coordinates)

Ventral Precuneus (0, -62, 24)  
Retrosplenial (6, -54, 10)

(Retrosplenial seeds more consistent then ventral precuneus seed - overlap in CSF)
Results

12 yo normal subject, awake

Retrosplenial seeds:

axial slices at -22, -12; -2; 8; 18; 28 mm, MNI space

Robust connectivity with the seed points was typically seen in fusiform gyri, parahippocampus and hippocampus.

Connectivity pattern was found to be bilateral and relatively symmetric in control subjects.
Results

2 yo normal subject, natural sleep

Pattern was observed in control subjects age 2 though adult.

Remains present in asleep and anesthetized subjects.
Results

14 yo patient L mesial temporal sclerosis

Awake

Connectivity  
R>>L

Retrospenial seeds
Results
21 yo patient Cystic lesion in the R temporal lobe with surrounding edema

Awake

Connectivity
Bilateral, R ≈ L

Retrosplenial seeds
Results
6 yo patient Parry Romberg syndrome and left sided seizures

Anesthetized (propofol)

Connectivity
R>>L
fcMRI assessment mesial temporal fxn:

Preliminary results suggest fcMRI could potentially be useful in preoperative mesial temporal function evaluation.

Need further understanding of the relationship between fcMRI and underlying cortical functionality.

Develop quantitative methods for analysis.

Correlate these fcMRI results with Wada testing, neuropsych and ultimately surgical outcomes.
Inter-hemispheric synchronicity of resting state BOLD spontaneous fluctuations:

Inter-hemispheric synchronicity of networks are disrupted in some pathologic states.

Potential for use in analyses to detect pathology which disrupts this synchronicity.
Functional connectivity: std space seeds.
11 yo healthy female subject

Connectivity patterns relatively symmetric
Inter-hemispheric connectivity:
2 year old male (under anesthesia), Dysplasia – L Hemispheric

Inter-hemispheric connectivity in SM network appears intact.
Disrupted inter-hemispheric connectivity in visual and DMN networks.
Inter-hemispheric connectivity:
3 year old female (under anesthesia), Sturge-Weber syndrome

Marked decrease in inter-hemispheric connectivity in SM network.
Reduced inter-hemispheric connectivity in visual and DMN networks.
Seizure/dysplasia focus identification using fcMRI:

- Is it possible to utilize the normal symmetry and the disruption of the symmetry in epilepsy to identify a focus of dysplasia?
Seizure/dysplasia focus identification using fcMRI:

- Normally fcMRI: strong interhemispheric connectivity between homotopic (geometrically corresponding) regions across the brain (strength can vary between regions)
- Voxel-Mirrored Homotopic Connectivity (VMHC) quantifies functional homotopy by providing a voxel-wise measure of connectivity between hemispheres by computing the connectivity between each voxel in one hemisphere and its mirrored counterpart in the other
Voxel-Mirrored Homotopic Connectivity (VMHC)

- Evaluated a series of 7 patients with FCD to characterize homotopic connectivity of dysplastic areas that were the seizure focus.
- 4 displayed dramatic reduction of homotopic connectivity in the FCD area, one showed moderate reduction and 2 did not show clear reduction.
FCD: MRI and ictal PET
FCD: MRI and ictal PET

- Seed [ ] rs fMRI at
- PET seizure focus
Voxel-Mirrored Homotopic Connectivity (VMHC)
Conclusions passive task and resting state:

- Passive task fMRI paradigms under anesthesia appear robust; perhaps to be supra-ceded by resting state fMRI.
- Resting state fMRI under anesthesia appears robust for mapping somatomotor, visual;
- As with clinical application of fMRI techniques in general, need further validation (correlate with cortical stimulation, outcomes).
- Resting state fMRI under anesthesia may also provide useful information in other functions of eloquent cortex: mesial temporal; possibly identify dysplasia
Summary:

- A. Goals of clinical fMRI in pediatric epilepsy
- B. Review basics of fMRI
- C. Challenges of fMRI in children
- D. Task based fMRI (active and passive) SM
- E. Task based fMRI Language
- F. Task based fMRI preliminary Memory work
- G. Resting state fMRI: potential/ future applications
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