FUNCTIONAL ASL: PERFUSION BASED FUNCTIONAL MRI USING ARTERIAL SPIN LABELING

APPLICATIONS OF ASL IN NEUROSCIENCE

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OVERVIEW

• Quick review of ASL
• The niche for ASL
• Examples of practical applications in literature
A generic ASL pulse sequence

Some Options
• Pulsed vs. Continuous
• Delays
• Saturation Pulses
• 2D, 3D …
CONTINUOUS ASL

Inversion & Control At the same location
PULSED ASL SCHEMES
VELOCITY SELECTIVE ASL
ASL-BASED FUNCTIONAL MRI

Raw (unsubtracted) time course
A LINEAR MODEL FOR ASL

- Base image
- BOLD effects
- ASL at rest
- ASL during activation
QUANTIFYING DYNAMIC PERFUSION CHANGES

Traditional Approach:
2. Calculate difference in perfusion between conditions.
3. Calculate means and variances

GLM Approach:
1. Translate GLM parameters (betas) into perfusion.
EVENT RELATED BOLD

An FMRI signal with Gaussian noise

[Graph showing an FMRI signal with Gaussian noise]

An FMRI signal with AR noise

[Graph showing an FMRI signal with AR noise]
An FMRI signal with Gaussian noise

An FMRI signal with AR noise
BLOCKED DESIGN FASL: SLOW PARADIGM

An ASL signal with Gaussian noise

An ASL signal with AR noise
BlocKed Design Fasl: Slow Paradigm

An ASL signal with Gaussian noise

An ASL signal with AR noise
ASL PERFUSION FMRI VS. BOLD (SENSITIVITY)

ASL PERFUSION VS. BOLD
VERY LOW TASK FREQUENCY

Treatment effects START in this range!

WHY ASL? QUANTIFICATION.

- BOLD: a complicated mix of parameters.
- Calibrated (quantitative) BOLD requires additional measurements (ASL is one of them).
- ASL can yield perfusion directly with simple calculation.
- Perfusion is well correlated with local field potentials and CMRO2.
- Perfusion is fairly stable from person to person.
- Multi-center studies.
- Longitudinal studies …
WHY ASL?
THE BOLD SIGNAL DRIFT

- Autoregressive structure of MRI noise
- BOLD signals are inherently “drifty” because:
  - Physiological effects
    - Respiration
    - Heart beat
  - Scanner effects
  - Temperature
WHY NOT ASL?

- Current ASL techniques have lower SNR than BOLD!
  - (the ASL signal is about 1 % of the total signal in a voxel)

- Current ASL techniques are significantly slower than BOLD!
  - BOLD can collect one volume every second
  - ASL requires a labeling period and a PAIR of images (3 seconds at the very best)
ASL'S NICHE

- Real time neurofeedback
- Drug Studies
- Attention
- Cognitive Training
- Low frequency paradigms
- Mental State studies
- Population Studies
- … anything SLOW or requiring Quantification!
SOME ASL STUDIES IN NEUROSCIENCE

• Cognitive neuroscience
  • Attention
  • Working memory
• Clinical applications
  • Schizophrenia
  • Multiple sclerosis
  • Alzheimers
EXAMPLE #1: SUSTAINED ATTENTION STUDY


• What are the neural substrates of sustained attention?
• What does distraction do to your ability to sustain attention?
• How does this relate to existing animal work (measures of cholinergic activity)?
SUSTAINED ATTENTION STUDY: THE EXPERIMENT

- Task paradigm:
  - Long period of time on task: 140 and 160 second blocks
  - Detect the presence of a short visual cue (< 50 ms).
  - Sometimes in the presence of a distracting flashing light.

- Imaging:
  - continuous ASL with separate labeling coil
  - No arterial signal suppression.
SUSTAINED ATTENTION STUDY: FINDINGS

- The distractor impaired behavioral performance.
- Increase in activation in right fronto-parietal regions.
- Recruitment of the mechanisms to maintain attention.
- But … RDLPFC correlates with worse performance.
- These results mirrored findings in rat studies of cholinergic system.

LUIS HERNANDEZ-GARCIA 2014, UM FMRI LABORATORY
SUSTAINED ATTENTION STUDY:

- Slow Paradigm (0.005 Hz)
- Intervention
- Longitudinal
- Baseline activity
- Quantification (relative)
EXAMPLE #2: WORKING MEMORY TRAINING STUDY


• How does cognitive training affect performance?
• What happens to your brain when you practice?
  • Resting
  • Activation
WORKING MEMORY TRAINING STUDY: THE EXPERIMENT

Visual N-back tasks: 4-back and 1-back
Imaging with pseudo-continuous ASL

1. Test Performance (while collecting ASL images)
2. Train for one week, 20 mins. per day
3. Test Performance (while collecting ASL images)
WORKING MEMORY TRAINING STUDY: FINDINGS

Effect of training: They get better at it

Visuospatial N-Back Performance

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Effect of training: They get better at it
WORKING MEMORY TRAINING STUDY: FINDINGS

Effect of training:
Resting Perfusion Change

Effect of training:
Activation Perfusion Change
WORKING MEMORY TRAINING STUDY:

✓ Intervention
✓ Longitudinal
✓ Baseline activity
✓ Quantification (relative)
EXAMPLE #3: SCHIZOPHRENIA STUDY


- Pharmaco-resistant auditory verbal hallucinations (AVH)
- People with AVH show increased activity in areas responsible for speech perception and production.
- What are the effects of repetitive TMS treatment?
SCHIZOPHRENIA STUDY: THE EXPERIMENT

- Neuronavigation (BOLD imaging of language processing)
- TMS treatment:
  - 10 day course
  - 1-Hz or theta-burst stimulation (TBS)
  - Neuronavigation with frameless stereotaxic system.
- Control group received usual (pharmacological) treatment
- Measure CBF before and after
- Measure psychotic symptom rating scale (psyRATS) before and after
SCHIZOPHRENIA STUDY: FINDINGS

ROI analysis: Reduced CBF in:
primary auditory cortex
Broca’s area
cingulate

Clinical: significant reduction in psyRATS with rTMS
SCHIZOPHRENIA STUDY:

- Intervention
- Longitudinal
- Baseline activity
- Quantification
EXAMPLE #4: MULTIPLE SCLEROSIS

D'haeseleer, M et al: “Cerebral hypoperfusion in multiple sclerosis is reversible and mediated by endothelin-1”
Proc Natl Acad Sci U S A. 2013 Apr 2;110(14):5654-8

- We know CBF is reduced in MS
- Chronic hypoperfusion can produce neuronal degeneration similar to MS
- Endothelin-1 (ET1) is a vasoconstrictor
- Is ET1 responsible for CBF reduction and neuronal damage?
- Therapy?
MULTIPLE SCLEROSIS STUDY:
THE EXPERIMENT

Protocol:
1. Measure CBF with pulsed ASL (EPISTAR)
2. Measure ET1 levels in internal Jugular vein
3. Administer ET-1 receptor antagonist: ‘bosentan’
4. Measure CBF with pulsed ASL (EPISTAR)
5. Measure ET1 levels in internal Jugular vein

Post-mortem histology in white matter samples from separate cohorts of controls and MS patients (ET-1 tests)
MULTIPLE SCLEROSIS STUDY: FINDINGS
MULTIPLE SCLEROSIS STUDY:

- Intervention
- Longitudinal
- Baseline activity
- Quantification (relative)
EXAMPLE #5: ALZHEIMER’S DISEASE

Hum. Brain Mapp.. doi: 10.1002/hbm.22522

- Hypo-perfusion precedes atrophy and dementia
- Find biomarker to predict outcomes: ASL and machine learning.
- ASL data and/or morphometry (GM atrophy)?
ALZHEIMER’S DISEASE STUDY: THE EXPERIMENT

- Two groups:
  - pre-senile patients with early stage dementia
  - ADNI cohort (elderly AD patients)
- pCASL imaging
- T1 weighted structural imaging
- Can we differentiate patients from controls using…
  - CBF?
  - GM volume?
  - Combination of the two?
- Compare several SVM classification methods
ALZHEIMER’S DISEASE STUDY: FINDINGS

CBF differences

GM volume differences
ALZHEIMER’S DISEASE STUDY: FINDINGS

- CBF could be used as a marker for diagnosis by itself
- No real added value in using CBF data for classification purposes
ALZHEIMER’S DISEASE STUDY: FINDINGS

Some interesting observations:
- CBF differences in amygdala
- GM differences in hippocampus
ALZHEIMER’S DISEASE STUDY:

- Intervention
  - ✓ Longitudinal
  - ✓ Baseline activity
  - ✓ Quantification (relative)
RECALL:

- Current ASL techniques have lower SNR and Speed than BOLD
- BOLD breaks down in slow paradigms because of drifts (autoregressive noise)
- Neurofeedback
- Drug Studies
- Attention
- Cognitive Training
- Slow paradigms
- Mental State studies
- Population Studies
- … anything SLOW or requiring Quantification!
QUESTIONS?