Advanced Clinical (F)MRI Applications of FSL

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Context of Clinical Applications

Single Patient Statistics
Clinical Decision-Making

Patient Group Statistics
Clinical Basic Research

Request and Reality

• direct, fast and reliable examination of the topography and integrity of "eloquent" neurofunctional systems under neuropathological conditions

• risk assessments for neurosurgical lesions, benefit prospects for "bionic" implant devices

• optimised surgical planning / neuronavigation (How and how far to operate?)

• MRI measures epiphenomena (BOLD / perfusion / diffusion) and is susceptible to false [esp. -negative] results (e.g. due to "decoupling" of neuronal from vascular responses, stealing phenomena etc.)

• limited performance, compliance, standardisation

• in vivo function ≠ lesion effect (reversible iatrogenic lesions: WADA, ESM)

• only few brain functions are "mappable" yet (black-box of several higher cognitive functions: [a]gnosias, [a]praxias)

Diseased Brains = Terra Incognita ?
**Attempts and Temptations**

- ALWAYS account for patient’s condition / history
- define presurgical questions / goals (rather system- than pathology-specific; but ALWAYS verify the diagnosis – see showcase 1 which was transferred as a tumor)
- answer the questions in an interdisciplinary and patient-friendly manner (requires neuropsychology, in proximity to the time & site of treatment under consideration)
- minimize risk for false-negatives (FN) (e.g. by combining BOLD + ASL, recording multiple „runs”, sensitising analysis & inference)

**Attempts and Temptations**

- mapping is considered “hip and sexy” (but is NOT necessarily to the advantage of your patient)
- potential source of illusive certainty vs. gratuitous apprehension (of imagers & surgeons involved)
- paradigm norms regardless of performance (in terms of tasks, speed & stimulus presentation; note: AMA’s CPT codes effective since 01/01/07)
- persuasiveness of self-fulfilling prophecies (mapping as “vicious circle”)

**Contraindications / Superfluous Maps**

- up to 80 % of mapping requests are medically **NOT** indicated
- absolute contraindication: emergencies
- relative contraindications: inevitable FN results
- superfluous maps: lesion topography and / or system (dis)integrity obvious by anatomical / clinical information; irrelevant for decision-making

**Absolute Contraindication**

clinical emergency: herniation due to midline shift & status epilepticus → no speech mapping!

(+ anterior temporal lobectomy relatively safe, Wernicke’s mostly dorsal to Heschl’s gyrus)
**Relative Contraindication**

FN inevitable: T2*-blackout in a cavernoma
(+ lesion obviously located at the intersection between superior / inferior precentral sulcus, slight & brief motor symptoms after microhemorrhage)

**Superfluous Maps (I)**

obvious topography: retrorolandic → no motor but possibly speech mapping
(Geschwind's territory* and arcuate tractography)

*Catani et al., Ann Neurol 2005 & PNAS 2007

**Superfluous Maps (II)**

obvious topography: paracentral metastasis → no motor mapping (contralateral leg already paretic)

**Artifacts / Lesion Coverage**

- bleedings, flow-void, drilling abrasions, calcinations etc. altering the EPI signal
  -> Make sure lesion is covered by analysis mask!
  Always look at original EPI (not just stats overlays on highres anatomical)!
  arterovenous malformation (AVM; hypointense flow-void)

intensity-masking (SPM) BET-mask (FSL)
Diagnostic Accuracy

<table>
<thead>
<tr>
<th>(F)MRI Result</th>
<th>Brain Property (Activity, Fibres, Perfusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>True-Positive (TP)</td>
</tr>
<tr>
<td>-</td>
<td>False-Negative (FN)</td>
</tr>
<tr>
<td>+</td>
<td>False-Positive (FP)</td>
</tr>
<tr>
<td>-</td>
<td>True-Negative (TN)</td>
</tr>
</tbody>
</table>

Clinical Accuracy Fallacies

- **FN fallacy**: insensitive data or / and analysis (e.g. lack of, delayed or paradoxical BOLD response due to pathological / immature vessels in tumors, FCDs, AVMs etc., perifocal edema, medication, esp. narcotics, in newborn...)
- **Thresholding**: no voxel is definitively "inactive"
- **FP fallacy**: controlling FP rates* is clinically inadequate – FN are the bogey! (*by assuming no activation & accepting only those voxels / clusters as active where this has to be rejected @ whatever p)

Statistical Inference

- **FP-protection**: multiple comparison correction (by FWER / FDR / TCFE...)
- **Directionality**: t- vs. F-Tests (always explore F-tests!)
- **TP-control**: Mixture Modelling (nonspatial / spatial)

What offers

- **FP-protection**: by FEAT, randomise, FDR, TCFE (by FWER / FDR / TCFE...)
- **Directionality**: contrasts / omnibus tests
- **TP-control**: (S)MM of MELODIC / FEAT results
- **FN-protection**: model- (FEAT) & data- (MELODIC) driven analyses; prethreshold masking; improved HRF-capturing (FLOBS, filmbabe, MELODIC --spca); perfusion modelling (FABBER) ...

...
Clinical Decision-Making

1. Is surgery promising and adequate?
2. How should it be performed?
3. Which specific risks will be associated with it?
   → informed consent, outcome prediction, aftercare plans

Recall: (F)MRI is NOT appropriate in medical emergencies. FMRI and (probabilistic) tractographies should be performed at the end of diagnostic patient evaluation, in proximity to time and site of the actual treatment.

Presurgical Localisation

• (sensori)motor & speech / language functions
• memory & visual functions (clinically questionable relevance)
• EEG-activity (predictive value uncertain), tractography, perfusion (all possibly in combination / conjunction with FMRI)
• functioning of the auditory system (prior to CI / ABI / AMI)

Showcase 1*: Motor Mapping

... is rarely indicated! (anatomic criteria usually define motor strip)

GLM: corr. p(FP) ≤ 0.05    p(TP)>0.80       PICA: p(TP)>0.80

FEAT     SMM    MELODIC

*Focal Cortical Dysplasia; see: Bartsch et al., JMRI 2006, for details

Showcase 2*: Speech Mapping

letter cued word generation = fluency test
(rather unspecific! here: < 5 words/min/letter)

left

Note: Language "wants" to be & stay left in most of all cases!

*left frontal glioma, see: Bartsch et al., JMRI 2006, for details
**Showcase 3**: Speech Mapping

word generation / nonfinal embedded clause sentences
Broca “phasotopie” in F3 (note: tumor is close to Exner’s speech area in F2)

**Note**: tumor access behind coronary suture

*left frontal glioblastoma; see: Bartsch et al., JMRI 2006, for details

**Showcase 4**: Speech Mapping

*sulcal AVM / left-handed; see: Bartsch et al., JMRI 2006, for details

**Special Considerations in AVMs**

- shunting reduces circulation time (calling oxygen supply by AVM vessels into question, e.g. by en-passage feeders)
- sulcal AVMs possibly easier to treat than gyral ones
- goal of embolisation & resection is cure
- mapping to clarify eloquence scores
- best prior to embolisation (embolisation introduces iatrogenic artifacts)

**Showcase 5**: Speech Mapping

*naming / nonfinal embedded clause sentences

*Bilateral language representations can dissociate (e.g. Wernicke’s from Broca’s) but are NOT necessarily equipotent!
(Rather, right coactivations are more often dispensable.)

*gyral AVM / left-handed; see: Bartsch et al., JMRI 2006, for details
Showcase 5: right temporal AVM

shunting by en-passant feeders, partial embolisation

after embolisation and after resection
(right coactivations were probably dispensable)

Showcase 6: Speech Mapping

False-negative BOLD result (overlay on T2-w background)...

left temporal AVM in an ambidexter; nonfinal embedded clause sentences

...but in this case (true-)positive ASL result (rare!).

Note: ASL seems reliable for simple sensory stimulation, motor tasks & RSNs but is less often successful in mapping higher cognitive functions.
"Messy" Maps vs. Complex Networks?

Speech mapping: same patient, different paradigms

- Reading nonfinal embedded clauses vs. covert auditory description-cued naming

Obstacles to Speech Mapping

- **classical** Wernicke-Geschwind model is out of date (language comprehension & production is modular & widely distributed in the brain)

- >10 cortical areas are involved (incl. LUOFG, Exner’s, Mill’s basotemporal language area*, Geschwind’s territory in the IPL, the lateral temporal lobe, anterior cingulum, SMA, anterosuperior insula ?, motor cortex, the non-dominant hemisphere…)

- Extracranial surgery beyond Broca’s & Wernicke’s area(s) as well as of lateralisation indices (LI) remains impossible to predict based on FMRI alone

- Arcuate tractography is supplementary (albeit damage to this fascicle does not necessarily cause conduction / repetition aphasia)

- Stimulation must be adjusted to patient abilities (key role of thorough + professional neuropsychological examination)

Showcase 7: Mapping of Memory Functions

- Hippocampal functions are lateralized (verbal memory more often & severely impaired after left-sided resections)
- FMRI less predictive than WADA* for lesion outcome

Showcase 8*: FMRI and Perfusion Mapping

- Simultaneous Motor and Baseline Perfusion-Map

  - PICA $p_{adj} \geq 0.67$
  - CBF $> 100 \text{ml/g/min}$

  - To account for most malignant tumor parts in the operation & at radiation

*superselective phenobarbital injection in PICA; HMPAO-SPECT / MRI
*right frontal glioblastoma; see: Bartsch et al., JMRI 2006, for details
Showcase 9*: Mapping Slow-Wave Foci

EEG / FMRI can be informative prior to tumor surgery!

Motor + interictal Slow-Wave BOLD-signature

right frontal glioma; see: Bartsch et al., JMRI 2006, for details

Showcase 10*: Mapping Sharp-Wave Foci

...and resolve inverse EEG-localisation errors.

Motor + Speech + interictal Sharp-Wave BOLD-signature

left parietal glioma; see: Bartsch et al., JMRI 2006, for details

Mapping pathological EEG-Activity

- technically very challenging, interictal activity does not provide best information about actual seizures
- FMRI can not extract a single definitely localised signature of an EEG focus.
- Thus, value for nonlesional epilepsy is very limited (since surgery of bihemispheric seizure foci is generally obsolete, FP would result in surgical contraindication).
- Therefore, it remains a quite investigative tool for clinical decisions!

Showcase 11*: FMRI and Tractography

Motor Mapping (BOLD) + Pyramidal Tractography

Intraoperative monitoring remains indispensible!
Showcase 12*: FMRI and Tractography

Motor Mapping (ASL) + Pyramidal Tractography (peduncular target) prior to (both sides) / after (just left) stereotactic biopsy.

Essential in subrolandic lesions: pyramidal tract can pass in front or/and behind.

*left subcentral cysticercosis; see: Bartsch et al., JMRI 2006, for details.

Showcase 13*: Tractography and Perifocal Edema

Probabilistic tractography enables tracking under aversive clinical conditions! *right parietomesial retro-rolandic glioblastoma

Somatotopy of the Pyramidal Tract

clinically important:
- fibre course from hand- vs. face area
- in the internal capsule

Note postcentral part of the pyramidal tract!

use of clinical apriori:
by normalising to "waytotal" or, alternatively, estimating the "constrained Bayesian model" (ref. on next slide).
Showcase 14*: FMRI and Tractography

Speech Mapping + Arcuate Tractography

*left temporal glioma; note Labbé’s vein as an anatomical marker

Showcase 15*: Arcuate Tractography

The arcuate fascicle is often viewed as part of the SLF (extension of its brachium anterius) but primarily follows the sulcus circularis insulae above the claustrum. Arcuate tractography is difficult and much facilitated by probtrack(X).

*left frontal low-grade glioma (F2) / motor agraphia

Showcase 16*: FMRI prior to "Bionic Implants"

*NF II, promontory test left cochlear implant (CI) in situ

*see: Bartsch et al., RoeFo 2002, for details

FMRI prior to Cochlear Implantation (CI)

- stimulus transmission to the auditory cortex = prerequisite for successful implantation
- auditory activations affirm stimulability
  - acoustically evoked: FMRI-audimetry
  - electrically evoked: FMRI-promontory testing
- applies also to brainstem & midbrain implants (BUT: ABI / AMI are above stimulation level, i.e. FN risk may be increased among candidates not eligible for CI)

*see: Bartsch et al., RoeFo 2002, for details

50 years of CI: Djouno & Eyries, La Presse Médicinale 1957
FMRI-Audiometry (I)

- EPI = loud(est) MR pulse sequence (up to 120 dB)
- EPI-noise primarily generated by Read-Outs [Gx]

→ only a disadvantage for FMRI?

See, for example, Haller et al., Allegma 2005

FMRI-Audiometry (II)

- EPI Read-Outs [boxes] evoke auditory activations*
- omission of ■ yields detectable BOLD-fluctuations#

HG = Heschl's gyr

See: Bartsch et al., Riv Neurosadiol'003/NeuroImage 2007, for details

FMRI-Audiometry (III)

<table>
<thead>
<tr>
<th>Subjects examined</th>
<th>definite hearing</th>
<th>FMRI-sensitivity</th>
<th>total deafness</th>
<th>FMRI-specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal hearing / awake (n = 60)</td>
<td>n = 60</td>
<td>97 %</td>
<td>none</td>
<td>-</td>
</tr>
<tr>
<td>hearing loss / awake (n = 36)</td>
<td>n = 33 (at least monaural residual hearing)</td>
<td>94 %</td>
<td>n = 2</td>
<td>100 %</td>
</tr>
<tr>
<td>hearing loss / sedated (n = 12)</td>
<td>n = 9</td>
<td>≥ 78 %</td>
<td>none</td>
<td>-</td>
</tr>
</tbody>
</table>

Bartsch et al., Kurt-Decker-Prize DGNR 2007

Showcase 17*:
FMRI-Audiometry prior to CI

= fast & irrespective of subjective report!

Patients with severe hearing loss are often unsure about their hearing percepts / impressions.

Furthermore, the method can also be used to demonstrate audition in psychogenic or factitious hearing loss.

*LVAS + Mondini; details in: Bartsch et al., JMRI 2006/NeuroImage 2007

Bartsch et al.
Showcase 18*: FMRI-Audiometry prior to CI

GLM cluster FWER-corrected p_{FWE}<0.05

right ear: left ear: deaf ?

Showcase 18*: FMRI-Promontory Testing prior to CI

Cochlear nerve present at all?

right ear: left ear: deaf not !
**History of Promontory Testing**

Alessandro Volta

'self-PT' ~ 1800

**Method of Promontory Testing**

- *extratympanic
- *transystmpanic

**Showcase 18**: Right FMRI-Promontory Testing prior to CI

- per se ear-selective, but hard to predict in GLM*
  (*"killer"-timecourses) \(\rightarrow\) PICA / MELODIC

**Showcase 19**: FMRI-Promontory Testing prior to CI

right aural deafness – right extratympanic promontory testing

Note the accompanying S2-(co)activations.

*see: Harms & Melcher, NeuroImage 2003: O(nset)S(ustained)O(ffset)R(amp)U(undershoot)
**Take-Home Messages**

- Clinical decision-making can utilise advanced FMRI applications. It ought to be patient-specific and interdisciplinary. Presurgical FMRI diagnostics differs between resective operations and insertion of bionic implant devices.

- Brain lesions may preserve functions but can nevertheless result in false-negative mappings.

- False-negative rates are reduced by analysing multiple modalities, runs and methods. However, reversible lesion tests (ESM / WADA) can not be replaced by (F)MRI.

**Coworkers and Cooperation Partners**

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