Advanced Clinical (F)MRI
Applications of FSL

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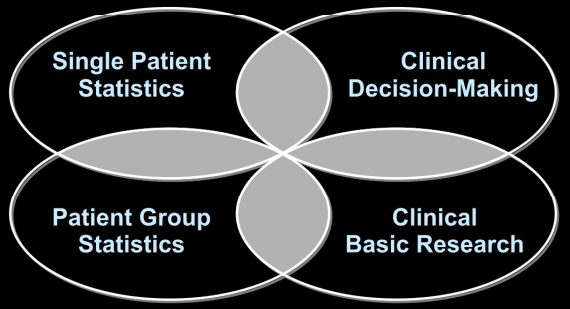
Context of Clinical Applications



Request and Reality

- direct, fast and reliable examination of the topography and integrity of "eloquent" neurofunctional systems under neuro-pathological conditions
- risk assessments for neurosurgical lesions, benefit prospects for "bionic" implant devices
- optimised surgical planning / neuronavigation
  (*How* and *how far* to operate?)

Request and Reality

- 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

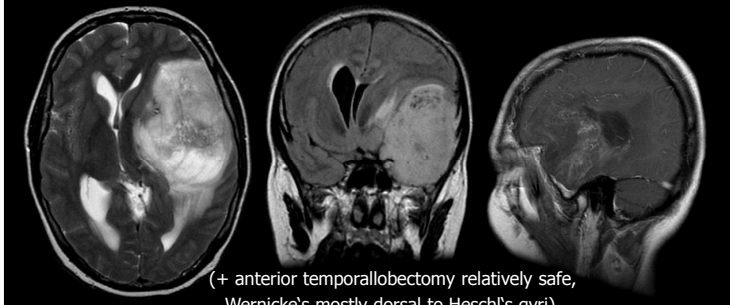
- mapping is considered "hip and sexy" (but is *NOT* necessarily to the advantage of your patient)
- potential source of illusive certainty vs. gratuitous apprehension (of imagers & surgeons involved)
- paradigm norms regardless of performance (in terms of tasks, speed & stimulus presentation; note: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

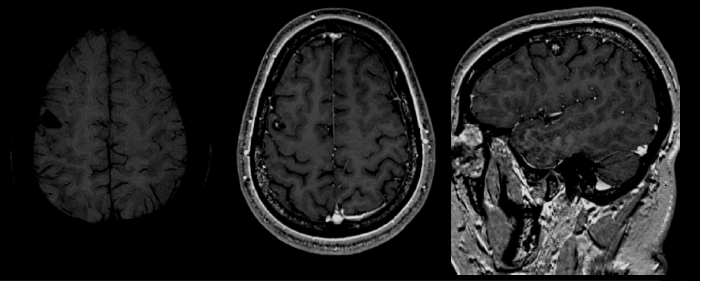


(+ anterior temporallobectomy relatively safe, Wernicke's mostly dorsal to Heschl's gyri)

Relative Contraindication

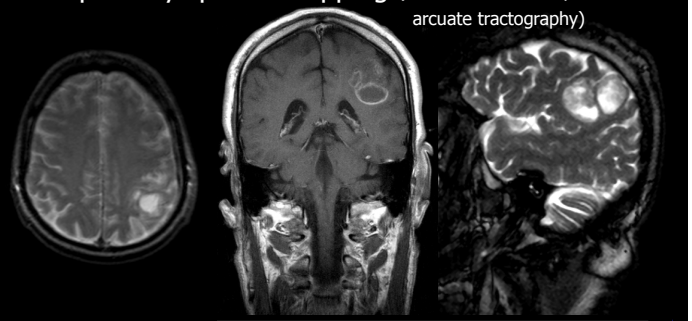
FN inevitable: T2*-blackout in a cavernoma

(+ lesion obviously located at the intersection between superior / inferior precentral sulcus, slight & brief motor symptoms after microhemorrhage)



Superfluous Maps (I)

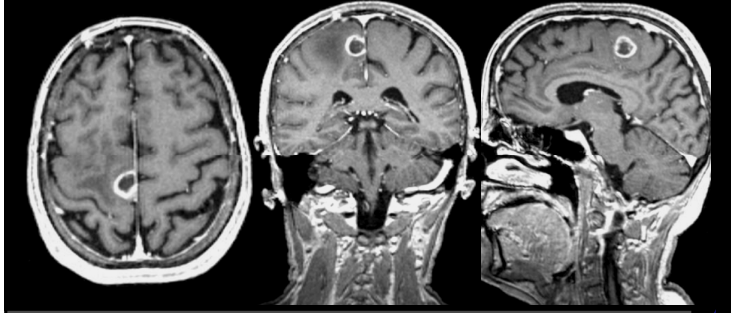
obvious topography: retrorolandic → no motor but possibly speech mapping (Geschwind's territory* and arcuate tractography)



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

Superfluous Maps (II)

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

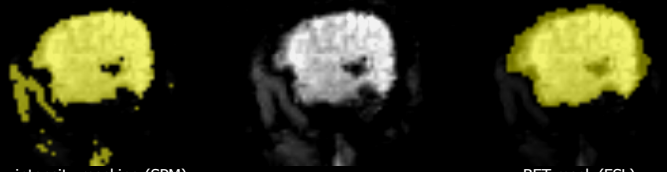


Artifacts / Lesion Coverage

- 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) *!*

arteriovenous malformation (AVM; hypointense flow-void)



intensity-masking (SPM)

BET-mask (FSL)

Diagnostic Accuracy

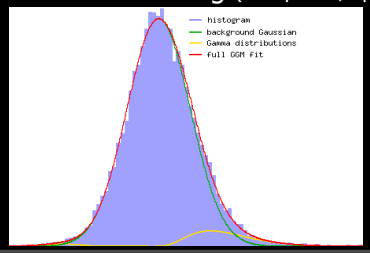
(F)MRI Result	Brain Property (Activity, Fibres,Perfusion)	
	+	-
+	True-Positive (TP)	False-Positive (FP)
-	False-Negative (FN)	True-Negative (TN)

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 FSL?

- 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.*

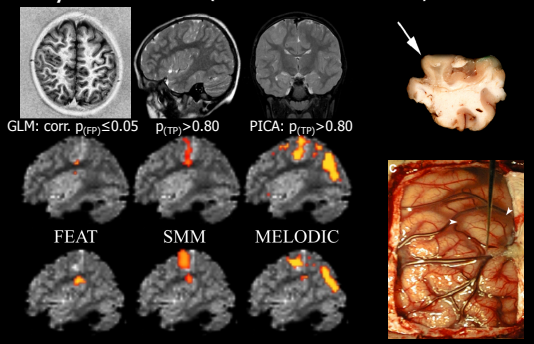
FMRI and (probabilistic) tractographies should be performed at the end of diagnostic patient evaluation, in proximity to time and site of the actual treatment.

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

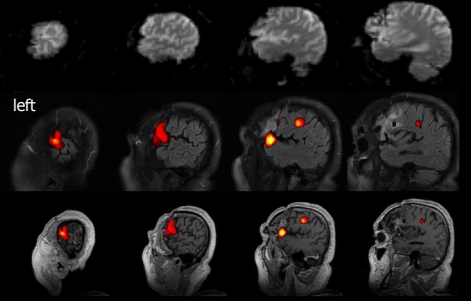
... is rarely indicated! (anatomic criteria usually define motor strip)



*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)



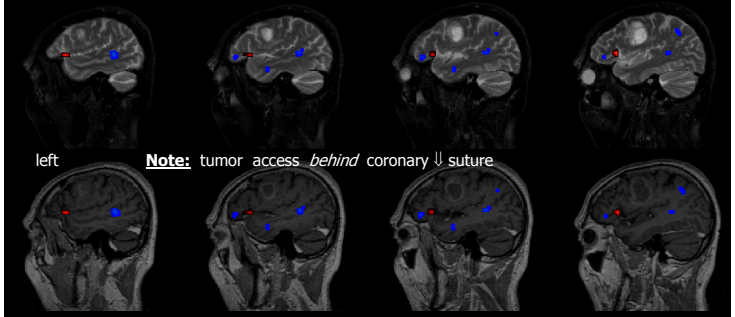
Note: Language "wants" to be & stay left in most of all cases!

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

Showcase 3*: Speech Mapping

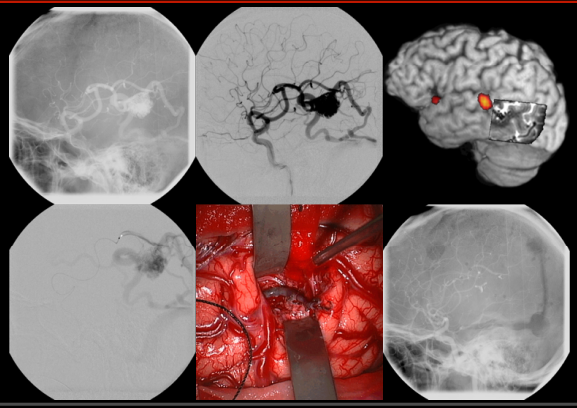
word generation / nonfinal embedded clause sentences

Broca-"phasotopie" in F3 (note: tumor is close to Exner's speech area in F2)



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

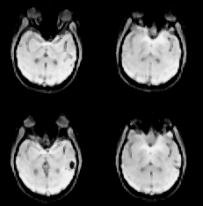
Showcase 4*: Speech Mapping



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

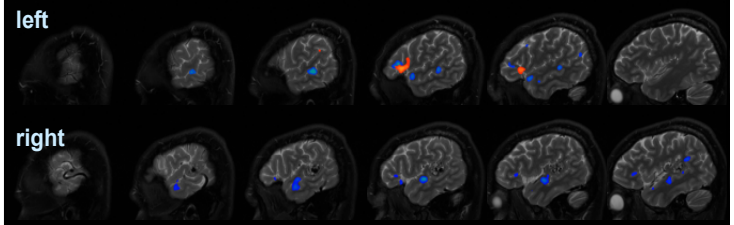
Special Considerations in AVMs

- shunting reduces circulation time (calling oxygen supply by AVM vessels into question, e.g. by en-passant 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

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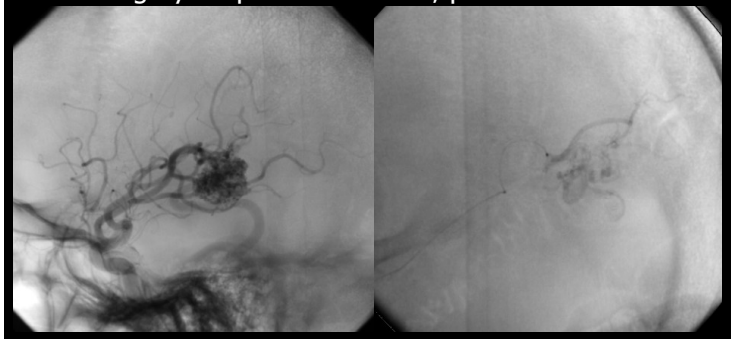
Showcase 5: right temporal AVM

shunting by en-passant feeders, partial embolisation



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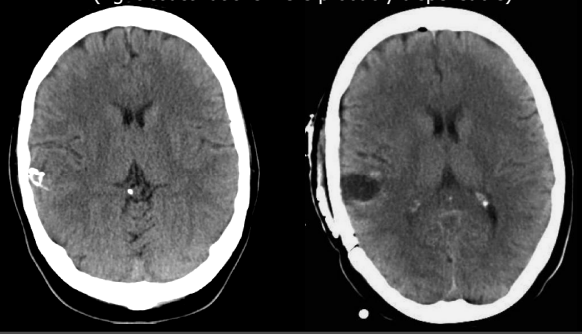
Showcase 5: right temporal AVM

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



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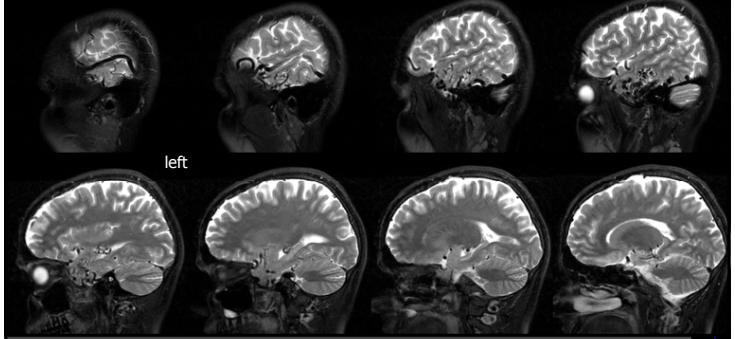
Showcase 6: Speech Mapping

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



left temporal AVM in an ambidexter; nonfinal embedded clause sentences

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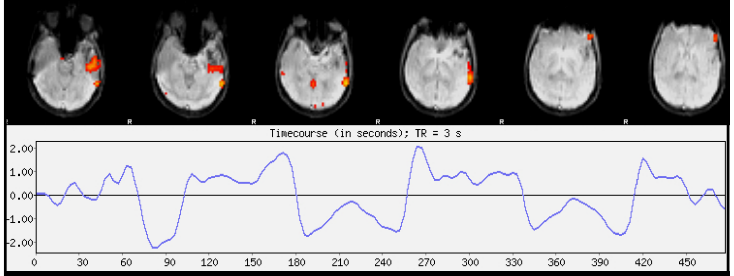
Showcase 6: Speech Mapping

...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.

PICA-MM $p_{(TP)}>0.80$

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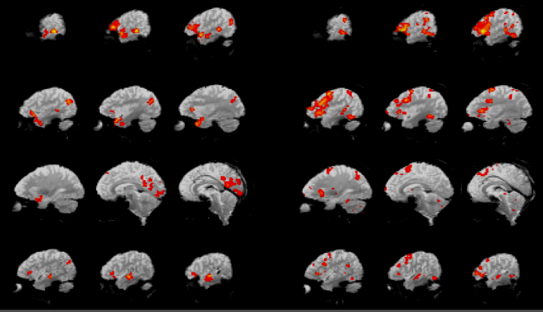
"Messy" Maps vs. Complex Networks?

Speech mapping: same patient, different paradigms

reading nonfinal embedded clauses *vs. covert auditory description-cued naming*



Obstacles to Speech Mapping

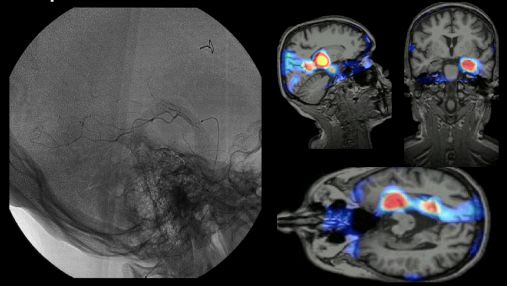
- classical Wernicke-Geschwind model is out of date
  (language comprehension & production is modular & widely distributed in the brain)
- >10 cortical areas are involved (incl. LI/OFG, Exner's#, Mill's basotemporal language area*, Geschwind's territory in the IPL, the lateral temporal lobe, anterior cingulum, SMA, anterosuperior insula ?, motor cortex, the non-dominant hemisphere…) ***BUT:*** surgical significance 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)

#Exner, *Braumüller* 1881; *Mills & Martin, *JAMA* 1912

Showcase 7: Mapping of Memory Functions

hippocampal functions are lateralized (verbal memory more often & severly impaired after left-sided resections)

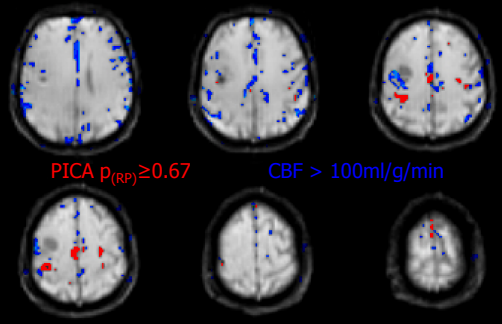
FMRI less predictive than WADA* for lesion outcome



*superselective phenobarbital injection in PCA; HMPAO-SPECT / MRI

Showcase 8*: FMRI and Perfusion Mapping

Simultaneous Motor and Baseline Perfusion-Map



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

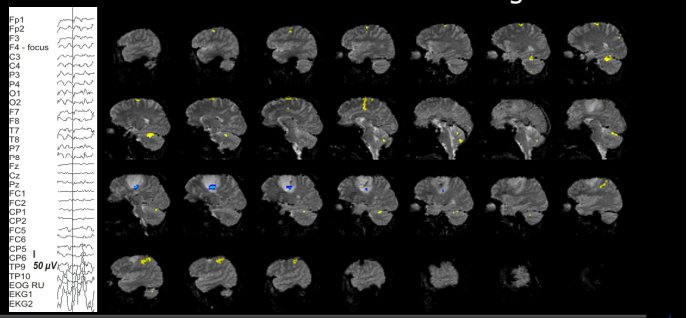
*right frontal glioblastoma; see: Bartsch et al., *JMRI* 2006, for details

Showcase 9*: Mapping Slow-Wave Foci

http://www.fmrib.ox.ac.uk/~rami/fmribplugin

EEG / FMRI can be informative prior to tumor surgery!

Motor + interictal Slow-Wave BOLD-signature



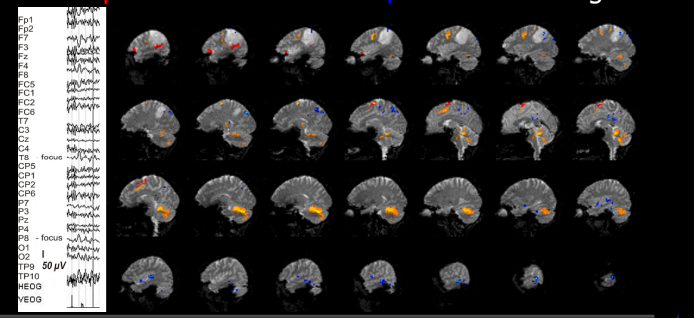
right frontal glioma; see: Bartsch et al., *JMRI* 2006, for details

Showcase 10*: Mapping Sharp-Wave Foci

http://www.fmrib.ox.ac.uk/~rami/fmribplugin

…and resolve inverse EEG-localisation errors.

Motor + Speech + interictal Sharp-Wave BOLD-signature



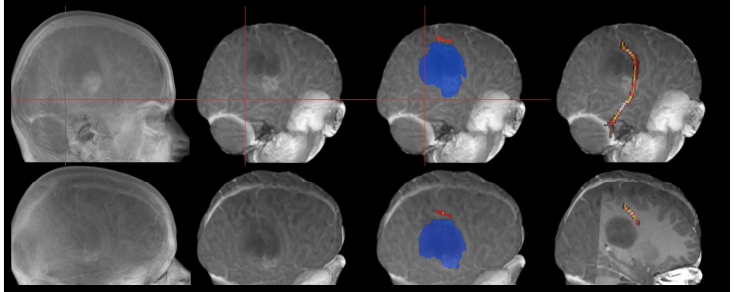
left parietal glioma; see: Bartsch et al., *JMRI* 2006, for details

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).
- Therfore, it remains a quite investigative tool for clinical decisions!

Showcase 11*: FMRI and Tractography

Motor Mapping (BOLD) + Pyramidal Tractography



Intraoperative monitoring remains indispensible!

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

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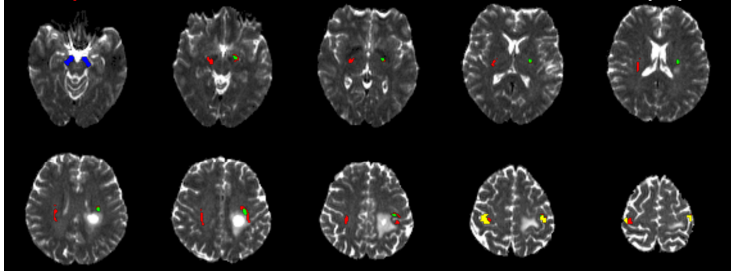
Showcase 12*: FMRI and Tractography

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

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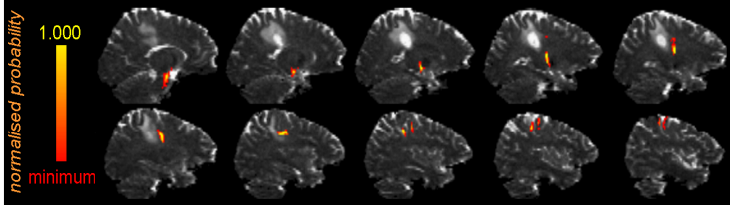
Showcase 12*: FMRI and Tractography

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



Note postcentral part of the pyramidal tract!

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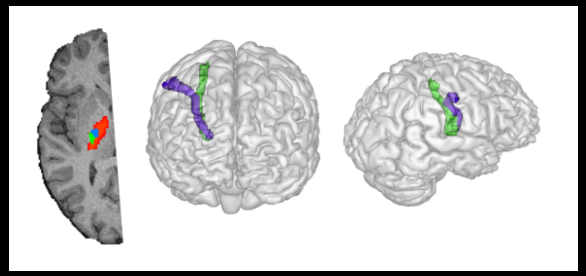
Somatotopy of the Pyramidal Tract

clinically important:
fibre course from hand- vs. face area



in the internal capsule

Jbabdi et al., *NeuroImage* 2007

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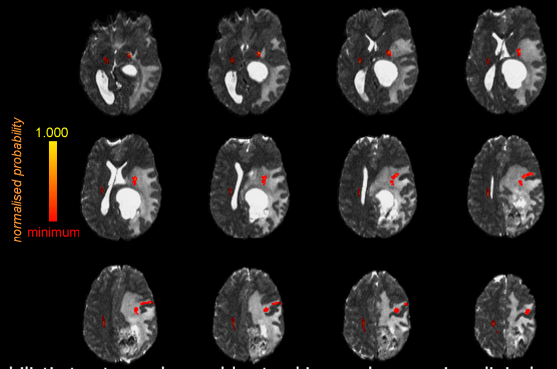
Showcase 13*: Tractography and Perifocal Edema



Probabilistic tractography enables tracking under aversive clinical conditions!

*right parietomesial retro-rolandic glioblastoma

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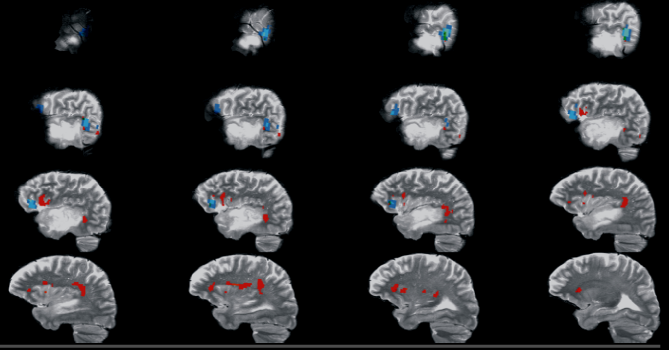
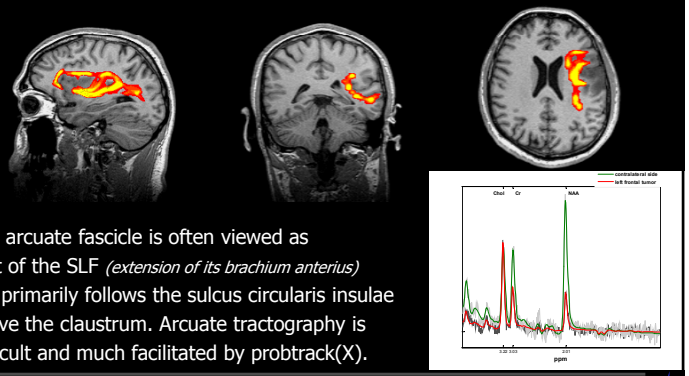
Showcase 14*: FMRI and Tractography

Speech Mapping + Arcuate Tractography



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

Showcase 15*: Arcuate Tractography

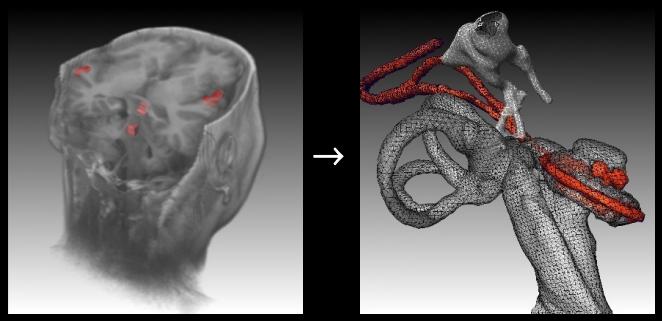


The arcuate fascicle is often viewed as part of the SLF *(extension of its brachium anterius)* but primarily follows the sulcus circularis insulae above the claustrum. Arcuate tractography is difficult and much facilitated by probtrack(X).

*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

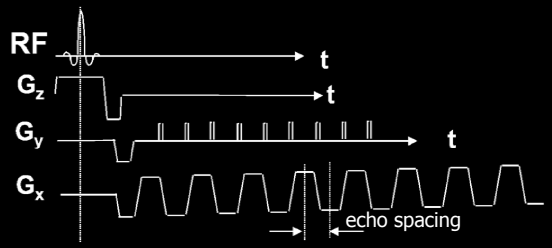
FMRI prior to Cochlear Implantation (CI)

- stimulus transmission to the auditory cortex = prerequisite for successful implantation
- auditory activations affirm stimulability
  - acustically evoked: FMRI-audiometry
  - 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)

50 years of CI: Djourno & 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 [G_x]

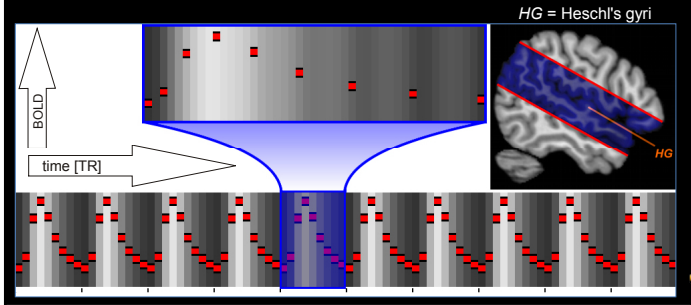


→ only a disadvantage for FMRI ?

see, for example, Haller et al., *Magma* 2005

FMRI-Audiometry (II)

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



see: Bartsch et al., * *Riv Neuroradiol* 2003/ # *NeuroImage* 2007, for details

FMRI-Audiometry (III)

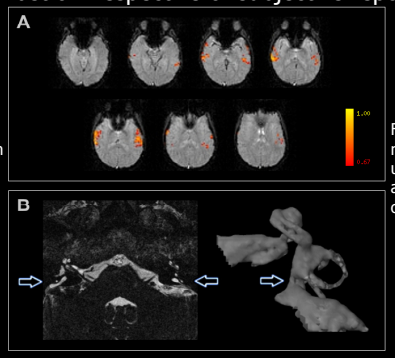
Subjects examined	definite hearing	FMRI-sensitivity	total deafness	FMRI-specificity
normal hearing / awake (n = 60)	n = 60	97 %	none	-
hearing loss / awake (n = 36)	n = 33 (at least monaural residual hearing)	94 %	n = 2	100 %
hearing loss / sedated (n = 12)	n = 9 (at least monaural residual hearing)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

Bartsch et al., *Kurt-Decker-Price DGNR* 2007

Showcase 17*: FMRI-Audiometry prior to CI

= fast & irrespective of subjective report !

Patients with servere 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

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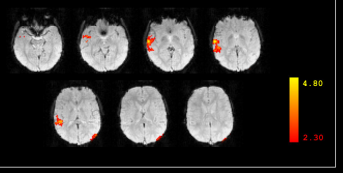
Showcase 18*: FMRI-Audiometry prior to CI

A

B



right ear: deaf

left ear: ?

GLM cluster FWER-corrected $p_{(FP)} \leq 0.05$

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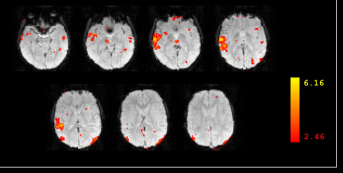
Showcase 18*: FMRI-Audiometry prior to CI

A

B



right ear: deaf

left ear: ?

GLM-MM $p_{(TP)} \geq 0.67$

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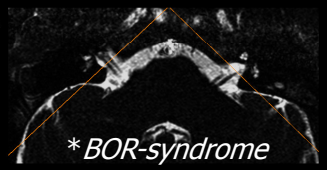
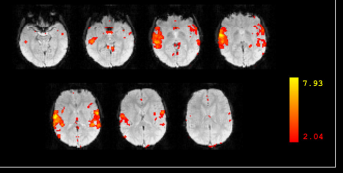
Showcase 18*: FMRI-Audiometry prior to CI

A



B



right ear: deaf

left ear: not !

PICA-MM $p_{(TP)} \geq 0.67$

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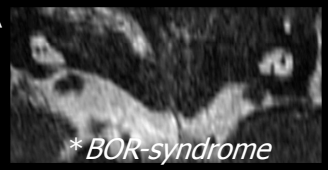
Showcase 18*: FMRI-Promontory Testing prior to CI

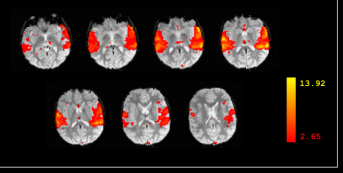
Cochlear nerve

A



present at all?

B



right ear: deaf !

left ear: not !

PICA-MM $p_{(TP)} \geq 0.67$, *right* extratympanic stimulation

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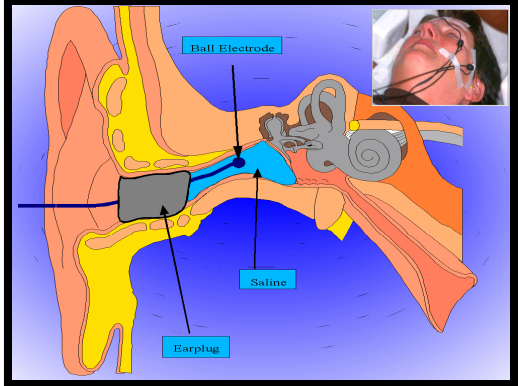
History of Promontory Testing

Alessandro Volta*

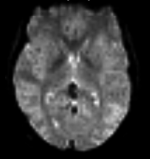
'self-PT' ~ 1800

*18.02.1745, Presbyacusis ?

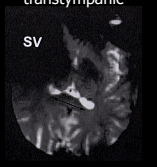
Method of Promontory Testing



*extratympanic



#transtympanic

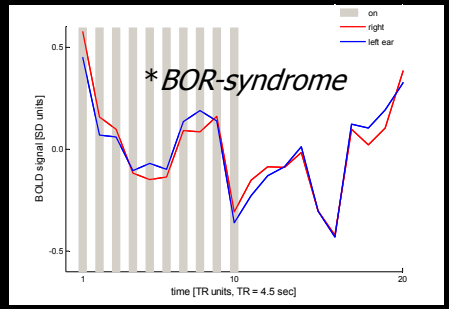


*Hofmann et al., *AJNR* 1999; #Obler et al., *MRM* 1999

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

- per se ear-selective, but hard to predict in GLM# ("killer"-timecourses) → PICA / MELODIC !

right ear: deaf !

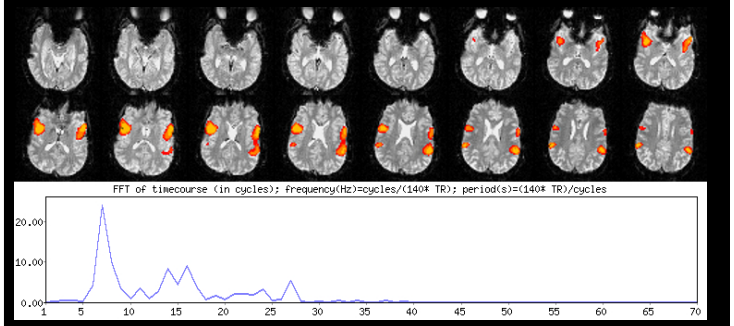


left ear: not!

#see: Harms & Melcher, *NeuroImage* 2003: $O_{(nset)}S_{(ustained)}O_{(ffset)}R_{(amp)}U_{(undershoot)}$?

Showcase 19*: FMRI-Promontory Testing prior to CI

right aural deafness – right extratympanic promontory testing



Note the accompanying S2-(co)activations.

*NF II; see: Bartsch et al., *JMRI* 2006, for details

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

Neuroradiology

- Georg Homola
- Armin Biller
- Martin Bendszus
- László Solymosi
- …

Neurosurgery, ENT, Neuropsychology, Physics

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FMRIB Oxford, Imperial College London:

- Christian F. Beckmann, Mark Woolrich, Timothy Behrens, Stephen M. Smith, Mark Jenkinson, …