#### **Cerebrovascular Reactivity Mapping - Promises and Pitfalls**

Cerebrovascular Reactivity Mapping (CVRM) has been promoted as an emerging standard of clinical care for presurgical assessment of:

a) the cerebrovascular reserve capacity in steno-occlusive arterial vasculopathies (arteriosclerotic macroangiopathy, Moya-Moya disease & similar disorders) and

**b)** peri- and intralesional (such as -tumoral) BOLD responsiveness prior or in addition to conventional task-, such as language-, or resting-state-fMRI.

CVRM is based on hypercapnia-induced BOLD or ASL signal changes, which exceed the neurogenic BOLD effect up to an order of magnitude. Hypercapnia can be readily evoked by breath-hold (BH) maneuvers.

**CVRM promises to detect (neuro-)vascular "uncoupling" (NVU)**: In steno-occlusive arteriopathies, insufficient perfusion and collateralization is presumed to lead to maximal vasodilation irresponsive to hypercapnic (and neuronal) stimulation requiring interventional or surgical revascularization. In intra-axial brain tumors exhibiting NVU, on the other hand, CVRM is expected to identify areas at high risk for false-negative detections by conventional fMRI and thereby patients requiring awake surgery with intra-operative cortical electrical stimulation mapping (ESM).

Here I will show that **time-to-peak (TTP) differences in dynamic susceptibility contrastenhanced (DSC) perfusion imaging may mimic NVU in CVRM while the cerebrovascular reserve and neurovascular coupling is actually preserved. More specifically, I will demonstrate that TTP delays of DSC perfusion match exactly BH-CO<sub>2</sub>-CVRM delays of the measured BOLD signal. Incomplete and incorrect modelling in the temporal domain is illustrated to cause false-negative inference of CVRM (<b>GLM pitfall**). Model-free analysis by ICA can overcome this fallacy, as in conventional fMRI, for which I will present additional clinical examples. Implications for paradigm design of clinical fMRI will be discussed. Generally, confirming NVU requires to demonstrate a lack of activation, i.e. failing to reject the null hypothesis, which is extremely challenging (statistical pitfall). CVRM is no universal remedy to avoid false-negative detections in clinical fMRI but is, instead, itself susceptible to these. Alone, it is therefore not yet ready to be declared a standard for clinical care. However, perfusion abnormalities translate directly into BOLD-fMRI, and there are good reasons to obtain perfusion data to complement each clinical fMRI study prior to CVRM. HBM 2019 – Educational Course Functional MRI in Clinical Practice: Applications, Methods, and Controversies

### Cerebrovascular Reactivity Mapping (CVRM):

#### **Promises and Pitfalls**

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## **Talk Outline**

#### Quizzing

- 1) What does CVRM promise?
- 2) How to perform CVRM, and are there alternatives?
- 3) How to analyze CVRM, and what are the pitfalls?
- 4) What to conclude from CVRM, and what not?
- Re-Quizzing



## Quiz 1 - What is CVRM ?

- 1. Mapping of the cerebrovascular response to exogenous, vasodilatatory, i.v. contrast agent (Carbogen®)
- 2. Mapping perilesional BOLD responsiveness to breath-hold (BH) maneuvers
- 3. Mapping BOLD- and/or CBF-responses to reversible vasodilatatory (*such as CO2-*) challenges

## Quiz 2 - Signal Changes in CVRM are:

- 1. Approximately 0.1 –1.0 % BOLD
- 2. Lower than in DSC-perfusion but normally higher than neurogenic BOLD
- 3. Blood Carbonation Level Dependent (BCLD, as opposed to BOLD)

## **Quiz 3 - Clinical Relevance of CVRM**

Attenuated/abolished CVR is thought to indicate need for:

- 1. Revascularization (direct or indirect extra- to intracranial = EC-IC arterial bypass, carotid endarterectomy CEA, stenting ...)
- 2. Intra-operative electrical stimulation mapping (ESM)
- 3. Both or nothing

## The Promise of CVRM:

#### To detect Neuro-Vascular Uncoupling (NVU) =

diminished or absent functional hyperemia (increase of CBV, CBF & blood oxygenation, i.e. BOLD as detected by fMRI) in response to neural activation

#### **Causes for NVU:**

- 1. Reduced Cerebrovascular Reserve Capacity (*CVRC;* how much brain perfusion can increase upon global stimulation) due to increased vasodilatation of the microvascular bed of one or all macrovascular arterial territories at baseline such as in steno-occlusive arteriopathies (or respiratory / metabolic disorders)
- Reduced / lack of / paradoxically reversed hemodynamic responses (such as BOLD upon local stimulation) due to pathological neoangiogenesis (tumors, AVMs), local vasodilation or vascular steal, for example, in / around brain lesions

## Clinical Relevance of CVRM: Steno-Occlusive Arteriopathies

NVU / reduced CVRC to prompt revascularization:



## **Clinical Relevance of CVRM:** Brain Lesions in Eloquent Locations

NVU / reduced CVR to prompt ESM:



"An evolving standard for clinical functional imaging" ?

AJNR 2015, 36: 7-13









### How to perform CVRM:

- T2\*-w, BOLD-sensitive 2D-GE-EPI (or ASL) time-series (~2-3mm isotropic, matched to task-/rs-fMRI acquisition; ~5-10min, possibly less for ASL)
- 5-10 hypercapnic challenges (end-expiratory vs. inspiratory breathholds, Carbogen® inhalation) for ~10-20 secs, alternate with ~40 secs rest
- Physiological patient monitoring (respiration belt & logging, endtidal or arterial pCO<sub>2</sub>)
- Supplemental: fieldmaping for disortion correction (by DE-GE or phase reversed SE-EPI), high-res. 3D-T1, DSC-perfusion (matched to CVRM & task-/rs-fMRI), MRA of extra- & intracranial brain-supplying arteries



Why not Carbonic Anhydrase Inhibitor Acetazolamid (Diamox®) for BOLD-CVRM ?

- 1. Long plasma half-life of 4-8 hrs
- 2. Intra-venous application
- 3. ICP/IOP elevation, risk for seizures

Case 1: 23yo Male



**Case 1:** Neurofibromatosis Type 1, left ACI/M1/A1-Stenosis due to Intimal Hyperplasia



left A2 collateralized by ACOM, left fetal PCOM below stenosis















RRF is slower than neuronal HRF, Respiration Volume per Time (RVT) convolution, e.g. by a Gaussian,  $\sigma$  = 21 secs, peak lag 5 – 16 secs Neuroimage 2008, 40: 644–654



# Case 1: How to analyze BOLD-CVRM ? Model (GLM) vs. Data-driven (ICA) Results

























## Lessons for CVRM from Steno-Occlusive Arteriopathies

- 1. Perfusion delays propagate directly into CVRM delays (consider CVRC only abnormal if reduced at / beyond it)
- 2. △TTPs may mimic NVU in CVRM model-driven analysis of CVRM data using a single regressor of interest is prone to type II errors (FN detections) or spurious deactivations (directionality misinterpretation); incorrect temporal modelling of any - e.g. delayed - fMRI responses can have such effect ("GLM pitfall")
- 3. TCD-VMR is a cheap, fast and easy, non-invasive and reliable alternative to determine "upstream" CVRC *as an indicator for revascularization need*

## Evidence for NVU in / around intra-axial Brain Lesions (e.g. Gliomas, Metastases)

- 1. Reduced / lack of CO<sub>2</sub>-CVR in / around lesion
- 2. Asymmetric, decreased BOLD signal fluctuations (task-evoked or @ rest; esp. despite preserved function) SCA



## BUT : Does this really reflect NVU ?

1. Neurogenic BOLD might be preserved despite attenuated / abolished CO<sub>2</sub>-RF / RRF or a locally exhausted CVR to CO<sub>2</sub> (*different stimulus !*)\*

Altered perfusion in pathological vessels in / around the lesion may cause FNs of CVRM (local ischemia & lactatacidotic vasodilatation, tumor neoangiogenesis of vessels lacking autoregulation, AVM steal etc.)

 Mass effect, infiltrative tumor, perifocal edema etc. may lead to less neuronal tissue within a given volume reducing BOLD while NVC is actually preserved \*J Cereb Blood Flow Metab 1994, 14: 742–8 Case 3: 26 yo Female, Oligodendroglioma WHO Grade II



















#### (Anti-)Correlation between Mean Arterial Blood Pressure, Hypocapnia and BOLD rs-fMRI



## What to conclude from CVRM, and what not ?

- 1. CVRM is generally performed to demonstrate a lack of territorial or peri-/lesional activation, i.e. a failure to reject H0, which is difficult to ascertain ("statistical pitfall").
- While CVRM may indicate reduced BOLD reactivity / NVU, it is itself based on (*largely*) <u>uncoupling CBF from</u> <u>CMRO</u><sub>2</sub> and susceptible to false-negative detections. Therefore, CVRM is not quite ready to be declared a "standard of clinical care" and should not preclude patients from language (or memory) fMRI.

# Hot Topics for CVRM:

- 1. How to account for local perfusion abnormalities ? (e.g. inhomogenous perfusion of high-grade brain tumors)
- 2. Do we observe dissociations between CBF-CVRM, BOLD-CVRM and neurogenic BOLD ? (esp. CVRM-negative cases with preserved neurogenic BOLD or vice versa)
- 3. Can CVRM indeed prompt clinical decisions ? (e.g. when and where to perform ESM)

#### Voxels with CO<sub>2</sub>-BOLD-CVRM < Neurogenic BOLD, Improved Localization by CVRM?



## **BOLD- vs. ASL-CVRM:**

- Low SNR of single ASL label-control difference images
- Temporal sampling of ASL is slower than für BOLD-EPI (due to the labelling involved)
- ASL generates perfusion-weighted images and, when proper calibration is possible, quantitative CBF maps
- ASL-CBF signal changes under vasodilatatory challenge much higher than for BOLD
- BOLD-CVRM more commonly performed than ASL-CVRM (because??)







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