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 contrast-enhanced (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_2-CVRM delays of the measured BOLD signal. Incomplete and incorrect modelling in the temporal domain is illustrated to cause false-negative inference of CVRM (**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

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 CO_2-)* 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)

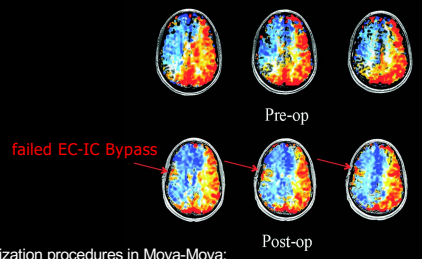
in response to neural activation

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)*
2. Reduced / lack of / paradoxically reversed hemo-dynamic 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:



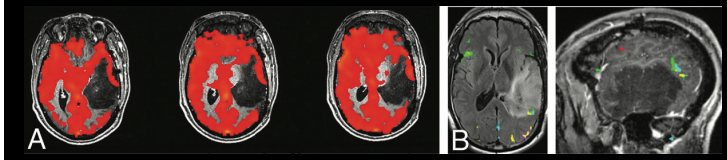
Revascularization procedures in Moya-Moya:

Direct STA-to-MCA(/ACA) bypass; indirect: encephaloduroarteriosynangiosis (EDAS), encephalomyoarterio-synangiosis (EMAS), encephaloarteriosynangiosis / pial synangiosis of STA

Stroke 2013, 44: S55–S57

Clinical Relevance of CVRM: Brain Lesions in Eloquent Locations

NVU / reduced CVR to prompt ESM:

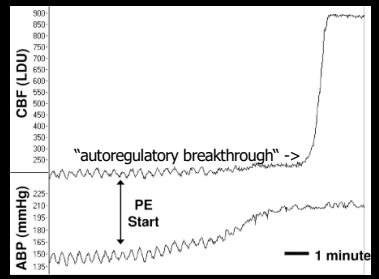


"An evolving standard for clinical functional imaging" ?

AJNR 2015, 36: 7–13

Autoregulation of CBF:

CBF of ~50-80ml/min*100g is maintained between ~60-160mmHg

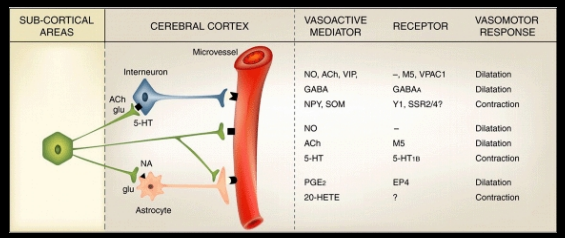


Microvascular hyperemia requires upstream arterial vasodilatation *(conducted, myogenic or flow-related?)* to avoid drop of downstream pressure

Hypertension 2007, 49: 334–340; *Circ Res* 1990, 66: 8–17

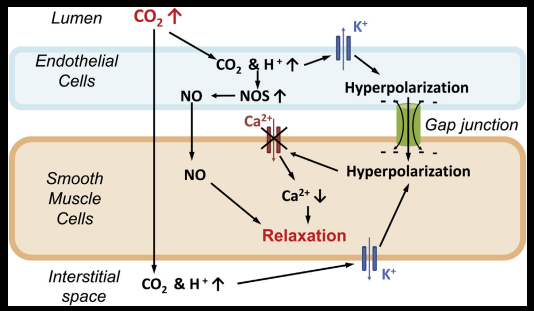
Glial Regulation of Local Neurovascular Responses:

Do astrocytes control local CBF more than neurons directly?



J Appl Physiol 2006, 100: 1059–1064

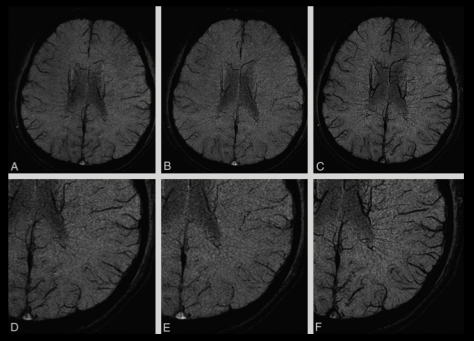
The Hypercapnic Response: Vasodilatation and ↑ CBF



5-7% CO_2 Inhalation increases CBF by ~75%

Neuroimage 2019, 187: 104–115; *J Clin Invest* 1948, 27: 484–492

Venographic Responses to Breath-Holds (B/E) & Hyperventilation (C/F):



BH->vasodilatation/↑CBF; HV->vasoconstriction/↓oxygenation

A/D = Baseline

AJNR 2014, 35: 1091–1095

How to perform CVRM:

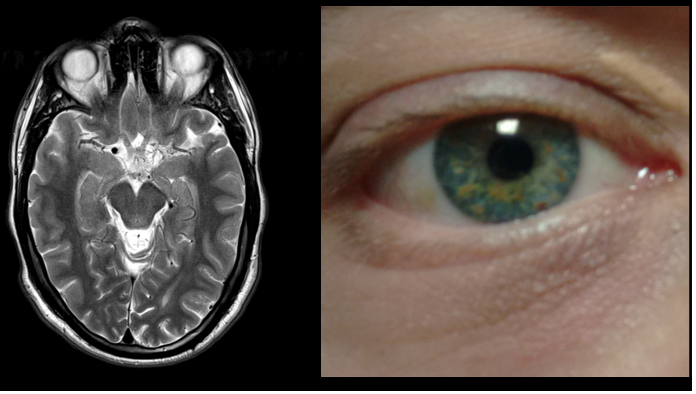
- T2*-w, BOLD-sensitive 2D-GE-EPI (or ASL) time-series *(~2-3mm isotropic, matched to task-/rs-fMRI acquisition; ~5-10min, possibly less for ASL)*
- 5-10 hypercapnic challenges *(end-expiratory vs. inspiratory breath-holds, Carbogen® inhalation)* for ~10-20 secs, alternate with ~40 secs rest
- Physiological patient monitoring *(respiration belt & logging, endtidal or arterial pCO_2)*
- 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

Poll

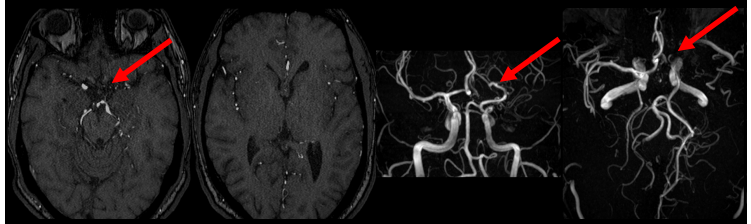
Why not Carbonic Anhydrase Inhibitor Acetazolamid *(Diamox®)* for BOLD-CVRM ?

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

Case 1: 23yo Male

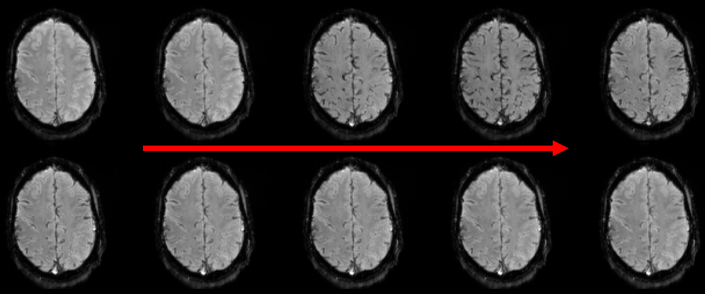


Case 1: Neurofibromatosis Type 1, left ACI/M1/A1-Stenosis due to Intimal Hyperplasia



left A2 collateralized by ACOM, left fetal PCOM below stenosis

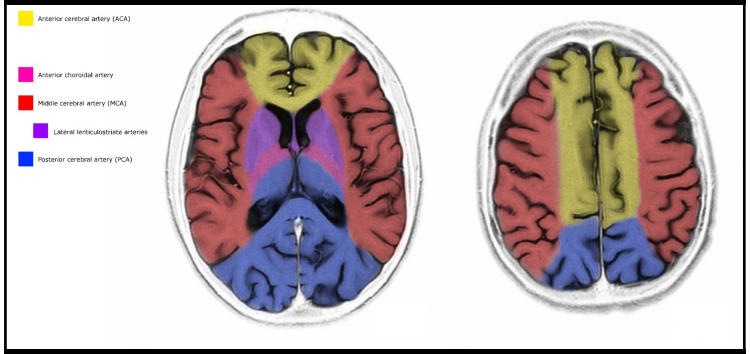
Case 1: DSC-Perfusion Signal Changes exceed BOLD-CVRM Signal Changes



Time

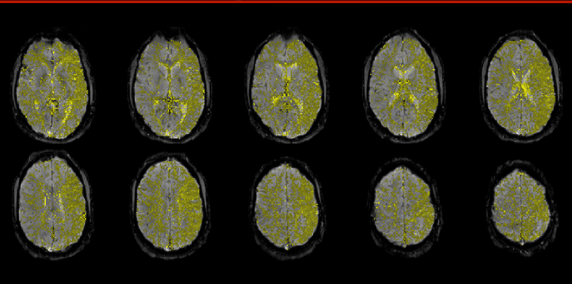
(1st lower row follows 5th upper row)

Arterial Territories of the Supratentorial Brain



courtesy of F. Gaillard, Radiopaedia.org, rID: 10814

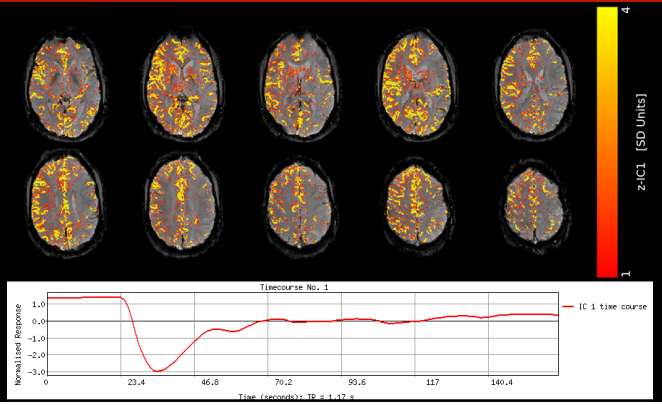
Case 1: DSC-Perfusion, Model-driven Time-to-Peak Delay *(based on Arterial-Input-Function AIF)* left MCA



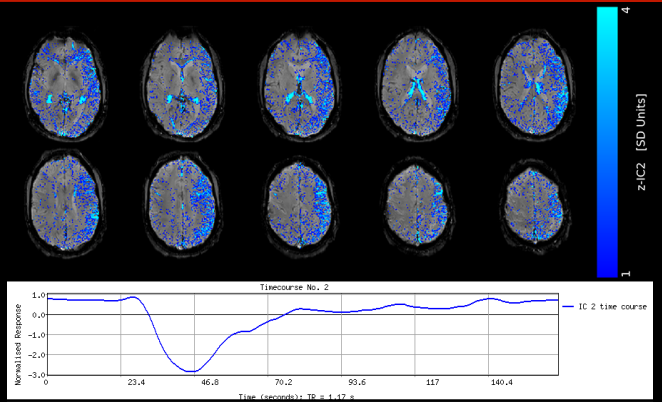
Questions to perform CVRM in this case:

1. Is there NVU due to reduced CVRC ?
2. Is revascularization by direct EC-IC bypass indicated ?

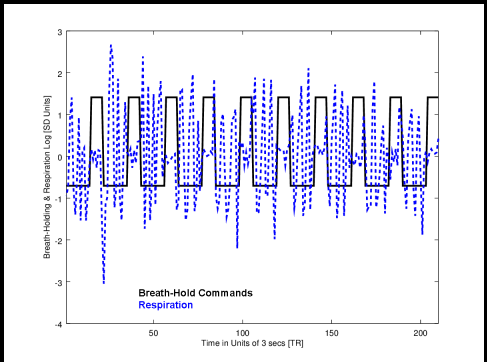
Case 1: DSC-Perfusion, Data-driven Independent Component 1 *(MELODIC, --spca; dip @ 36 secs)*



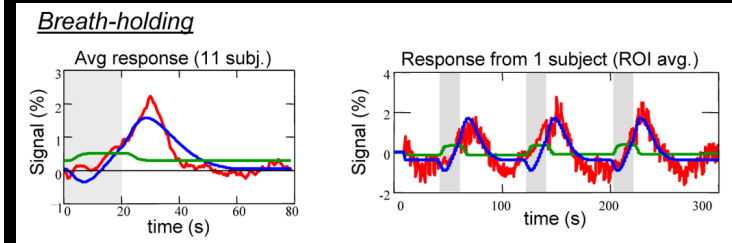
Case 1: DSC-Perfusion, Delayed IC 2 *(MELODIC, --spca; dip @ 47 secs)* left MCA-Territory



Case 1: How to analyze CVRM ? Confirm Compliance with BH-Commands:



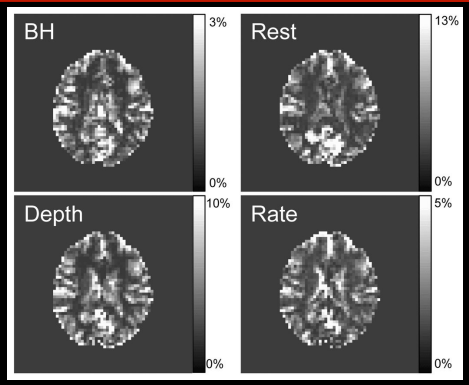
How to model BOLD-CVR ? CO_2-/Respiration-Response-Function (RRF):



RRF is slower than neuronal HRF, Respiration Volume per Time (RVT) convolution,
e.g. by a Gaussian, σ = 21 secs, peak lag 5 – 16 secs

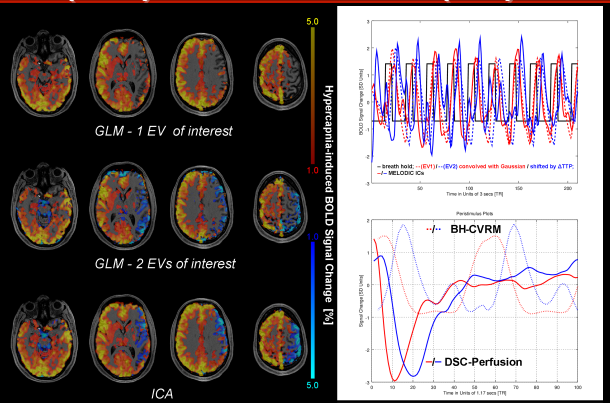
Neuroimage 2008, 40: 644–654

Respiration-induced BOLD Signal Changes

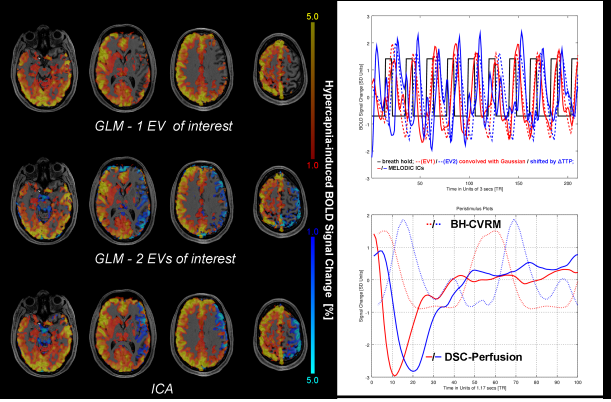


Neuroimage 2008, 40: 644–654

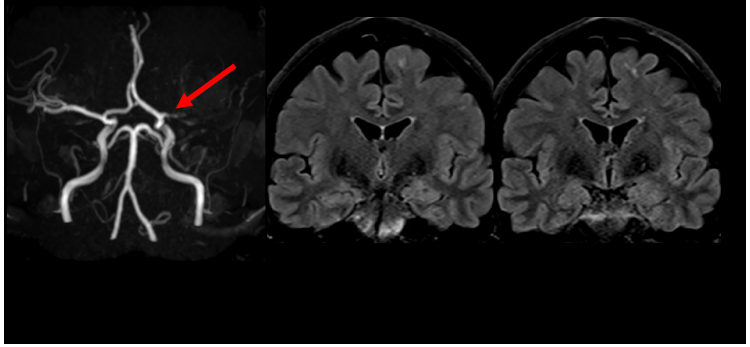
Case 1: How to analyze BOLD-CVRM ? Model (GLM) vs. Data-driven (ICA) Results



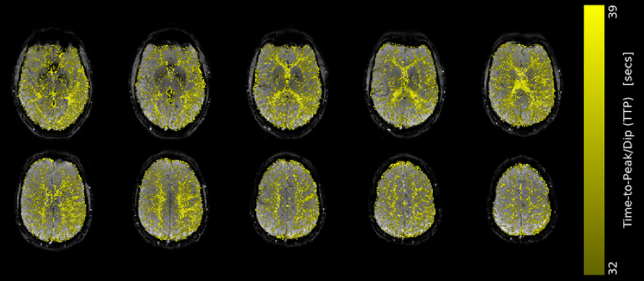
False-negative GLM with single EV, DSC-Delay matches BOLD-CVRM-Delay



Case 2: 50yo Female, Moya-Moya-Disease with left M1-Stenosis



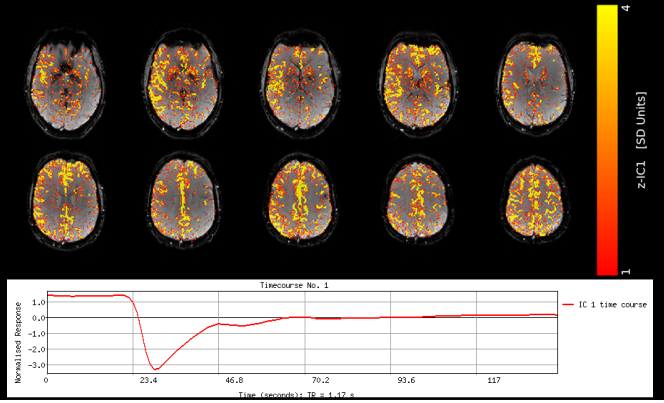
Case 2: DSC-Perfusion, Model-driven Time-to-Peak Delay *(based on Arterial-Input-Function AIF)* left MCA



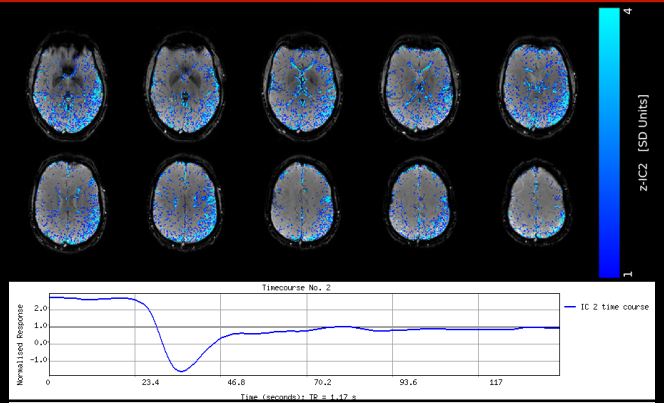
Same Questions to CVRM in this case:

1. Is there NVU due to reduced CVRC ?
2. Is revascularization by direct EC-IC bypass indicated ?

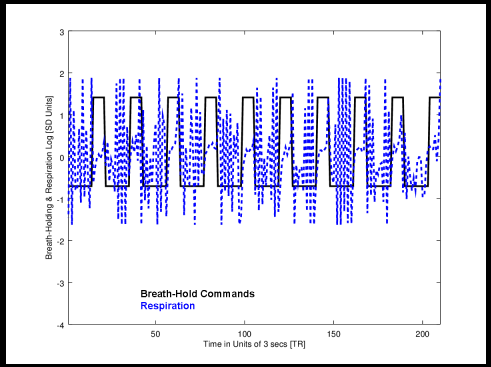
Case 2: DSC-Perfusion, Data-driven Independent Component 1 *(MELODIC, --spca; **dip @ 30 secs**)*



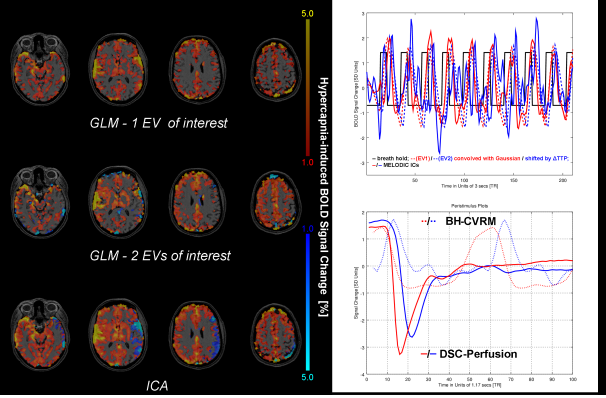
Case 2: DSC-Perfusion, Delayed IC 2 (MELODIC, --spca; dip @ 37 secs) left MCA-Territory



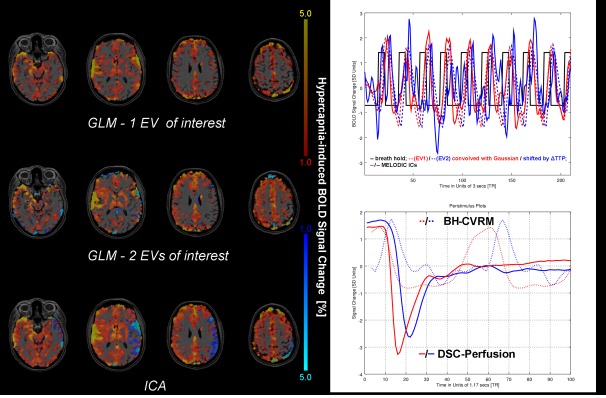
Case 2: Compliance with BH-Commands



Case 2: Model- (GLM) vs. Data-driven (ICA) Results of BOLD-CVRM

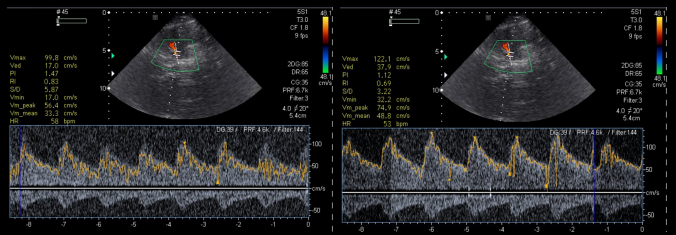


Again: False-negative GLM with single EV, DSC-Delay matches BOLD-CVRM-Delay



Case 2 - Alternative to CVRM:
Transcranial Duplex (TCD) Vasomotor Reserve (VMR)

Left poststenotic MCA, > 33 % VMR *(Vm_peak)* under Carbogen®



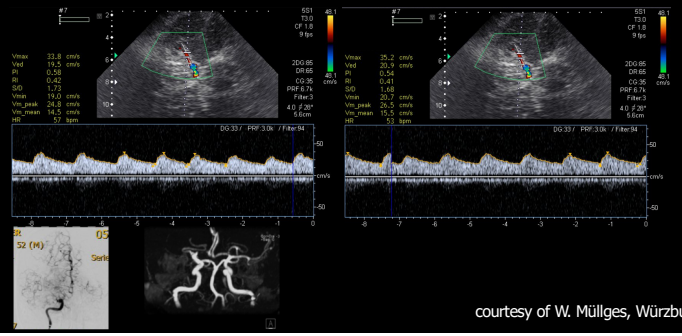
Normal VMR = 30 – 60 % in steady-state

Other CBF-based methods: ASL-MRI, SPECT, PET

courtesy of W. Müllges, Würzburg

Alternative to CVRM:
Reduced TCD-VMR in another Moya-Moya-Case

Right poststenotic MCA, < 7 % VMR *(reduced)*



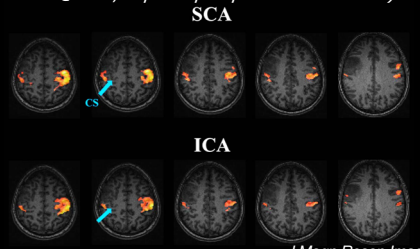
courtesy of W. Müllges, Würzburg

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_2-CVR in / around lesion
2. Asymmetric, decreased BOLD signal fluctuations
   (task-evoked or @ rest; esp. despite preserved function)



J Magn Reson Imaging 2016, 43: 620–626

BUT : Does this really reflect NVU ?

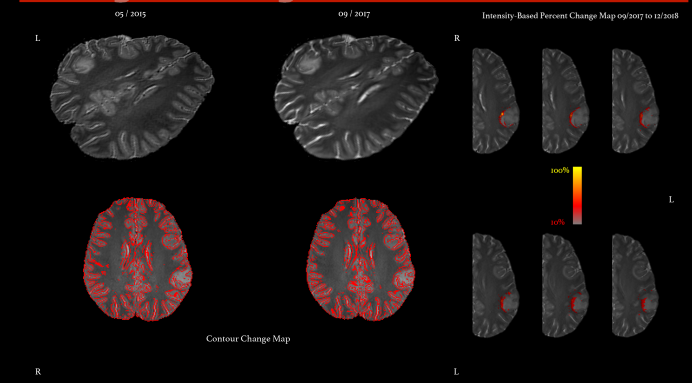
1. Neurogenic BOLD might be preserved despite attenuated / abolished CO_2-RF / RRF or a locally exhausted CVR to CO_2 *(different stimulus !)**

   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.)*

2. Mass effect, infiltrative tumor, perifocal edema etc. may lead to less neuronal tissue within a given volume reducing BOLD while NVC is actually preserved

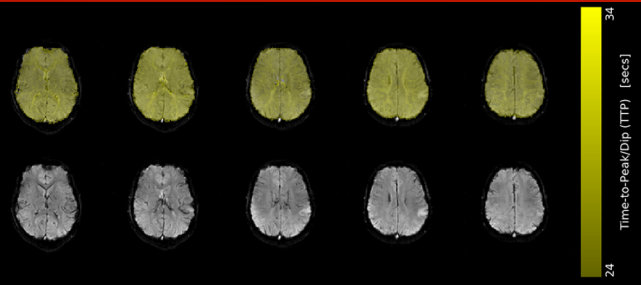
** J Cereb Blood Flow Metab 1994*, 14: 742–8

Case 3: 26 yo Female, Oligodendroglioma WHO Grade II



cf. Neuroimage 2010, 53: 1181–1196; *J Neurooncol 2014*, 118: 123–129

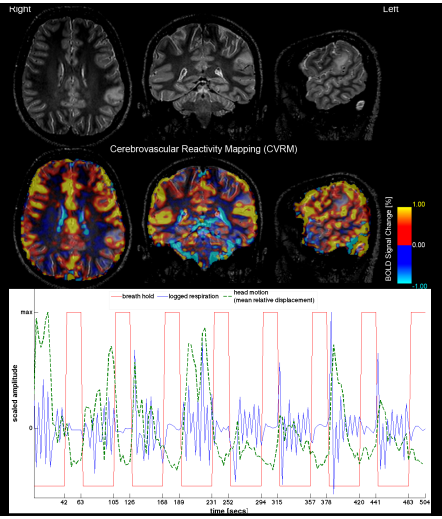
Case 3: DSC-Perfusion, No Intra-/Peri-Tumoral Time-to-Peak Delay *(based on Arterial-Input-Function AIF)*



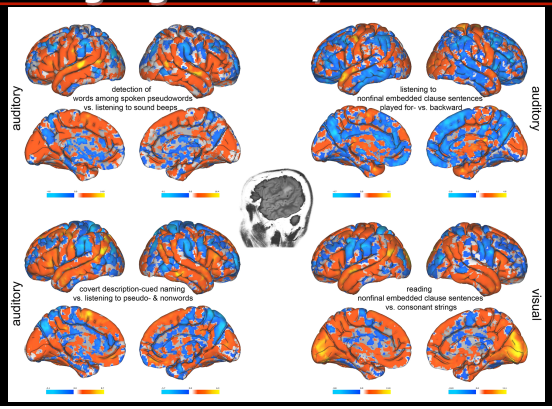
Different scenario to perform CVRM in this case:

1. Is there NVU / an increased fMRI FN risk in / around the lesion ?
2. Is ESM required / indicated during the resection ?

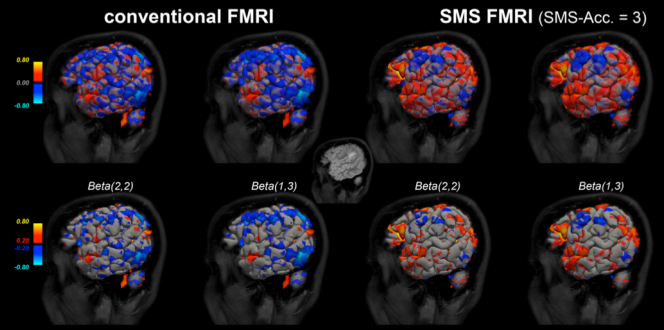
Case 3: BH-BOLD-CVRM



Case 3: 26 yo Female, 4 Language-Tasks / fMRI-Results



Case 3: Applying a Spatially Adaptive, Conditionally Autoregressive Model

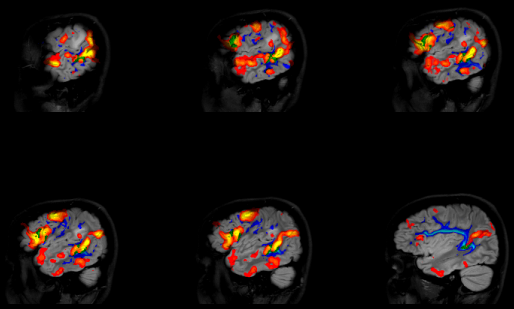


TR = 3.0 s, n = 160
3.0x3.0x3.0 mm (64x64)

TR = 1.5 s, n = 320
1.8x1.8x1.8 mm (120x120)

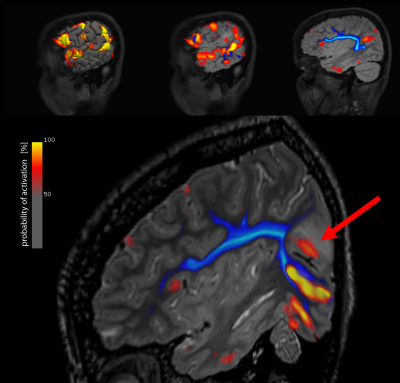
Bayesian Anal 2016, 11: 599–625

Case 3: ICA-based SMG*-Activations of Phonological Challenge (& Diffusion-Tractography)



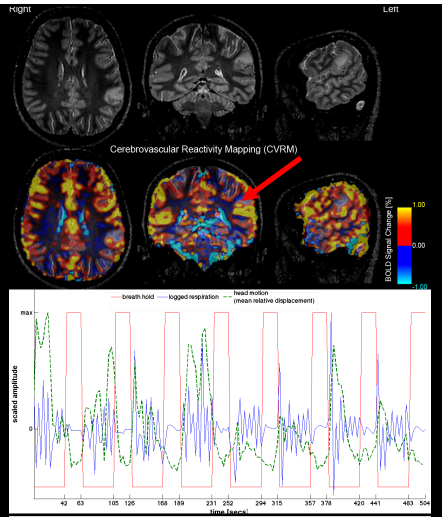
*SMG = supramarginal gyrus = Spt / Sylvian Fissure, parieto-temporal boundary

Case 3: ICA-based SMG*-Activations of Phonological Challenge (& Diffusion-Tractography)

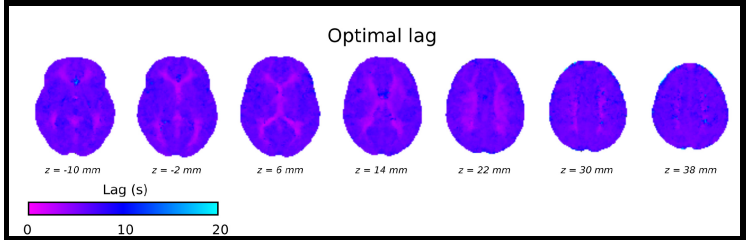


*SMG = supramarginal gyrus = Spt / Sylvian Fissure, parieto-temporal boundary

Case 3: BH-BOLD-CVRM revisited



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



to explain periventricular WM BOLD-CVRM deactivations based on Monro-Kelli doctrine?

Neuroimage 2014, 87: 287–296; *Front Neurosci 2019*, 13: 433

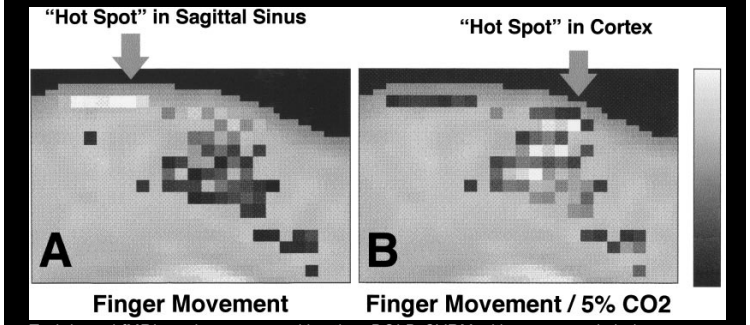
What to conclude from CVRM, and what not ?

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").*
2. While CVRM may indicate reduced BOLD reactivity / NVU, it is itself based on *(largely)* uncoupling CBF from $CMRO_2$ 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_2-BOLD-CVRM < Neurogenic BOLD, Improved Localization by CVRM?



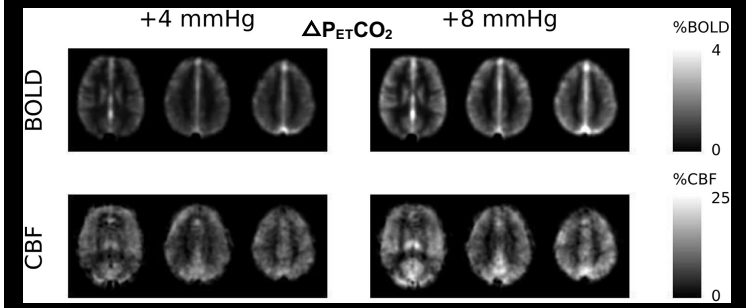
- Task-based fMRI can be more sensitive than BOLD-CVRM with some voxels being more responsive to neurogenic than vasodilatatory BOLD – *Does that question the utility of CVRM?*
- Issue of "calibrated" BOLD

NMR Biomed 1997, 10: 197–203

BOLD- vs. ASL-CVRM:

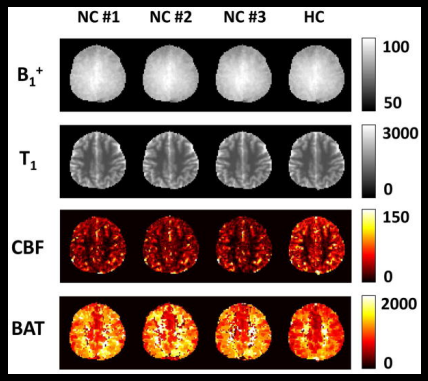
- Low SNR of single ASL label-control difference images
- Temporal sampling of ASL is slower than für BOLD-EPI *(due to the labelling involved)*
- ASL generates perfusion-weighted images and, when proper calibration is possible, quantitative CBF maps
- ASL-CBF signal changes under vasodilatatory challenge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

BOLD- vs. ASL-CVRM:



Front Neurosci 2017, 11: 276

Outlook: ASL-based CBF-/BOLD-CVRM, for example by MRF ?



Magn Res Med 2018, 75: 1812–1823

Re-Quiz

Re-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 CO_2-)* challenges

Re-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)

Re-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