"Du BOLD dans la matière blanche ?? Une revue de littérature"

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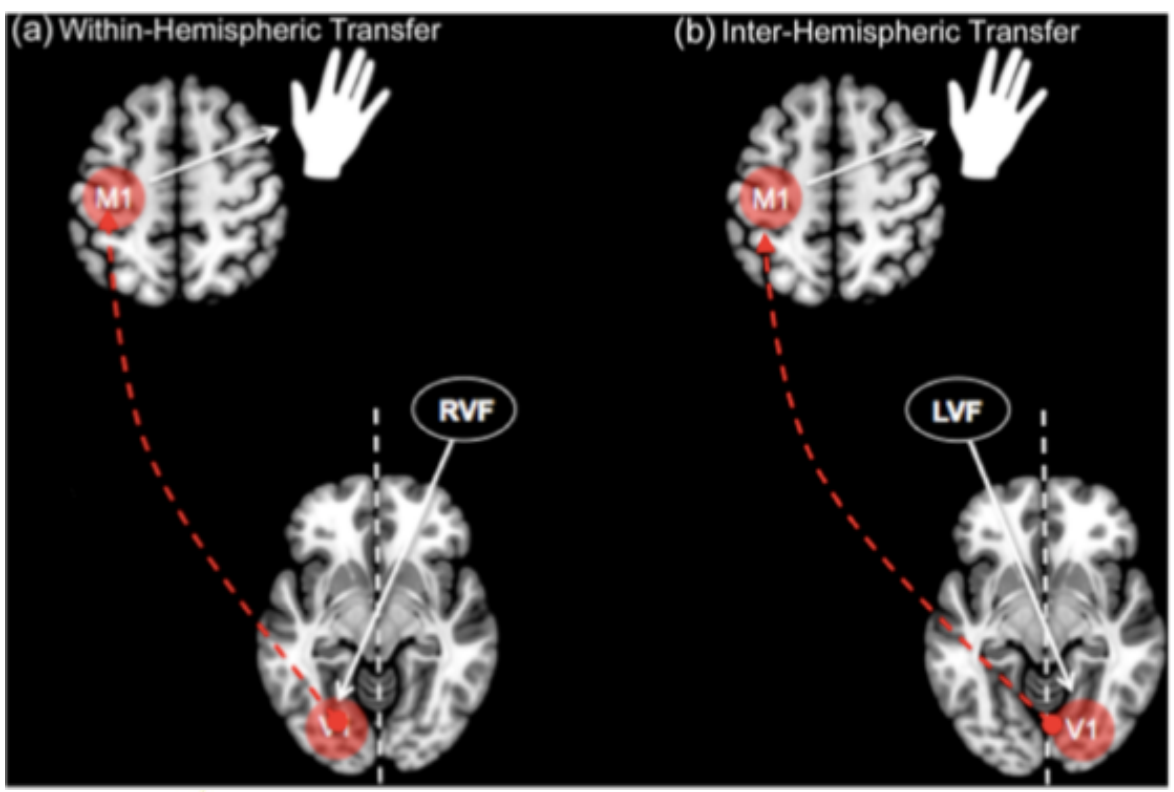
Outline

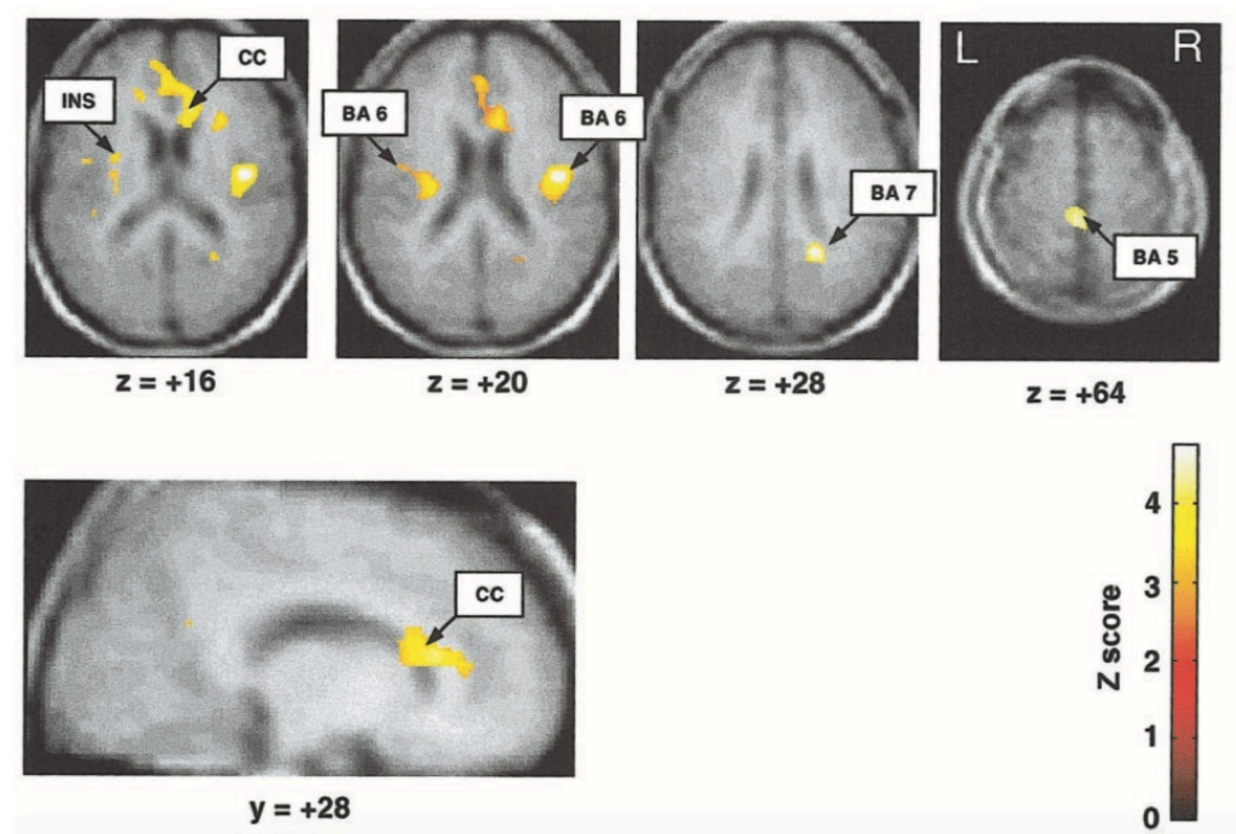
- Observation & debate
- Assumed physiological principles
- Evidence
- Implication
- Conclusions

Historical observation of BOLD in WM

- Maldjian et al. (1999) revealed WM activation in motor task at 4T but not at 1.5T.
- Brandt et al. (2000) found a negative signal change in the occipital white matter containing the optic radiations contralateral to the visually stimulated hemisphere.
- Mosier and Bereznaya (2001) found a direct activation of the corpus callosum during swallowing.
- Tettamanti et al. (2002) and several others reported Corpus Callosum activation during interhemispheric transmission of visuomotor information (Poffenberger's paradigm)

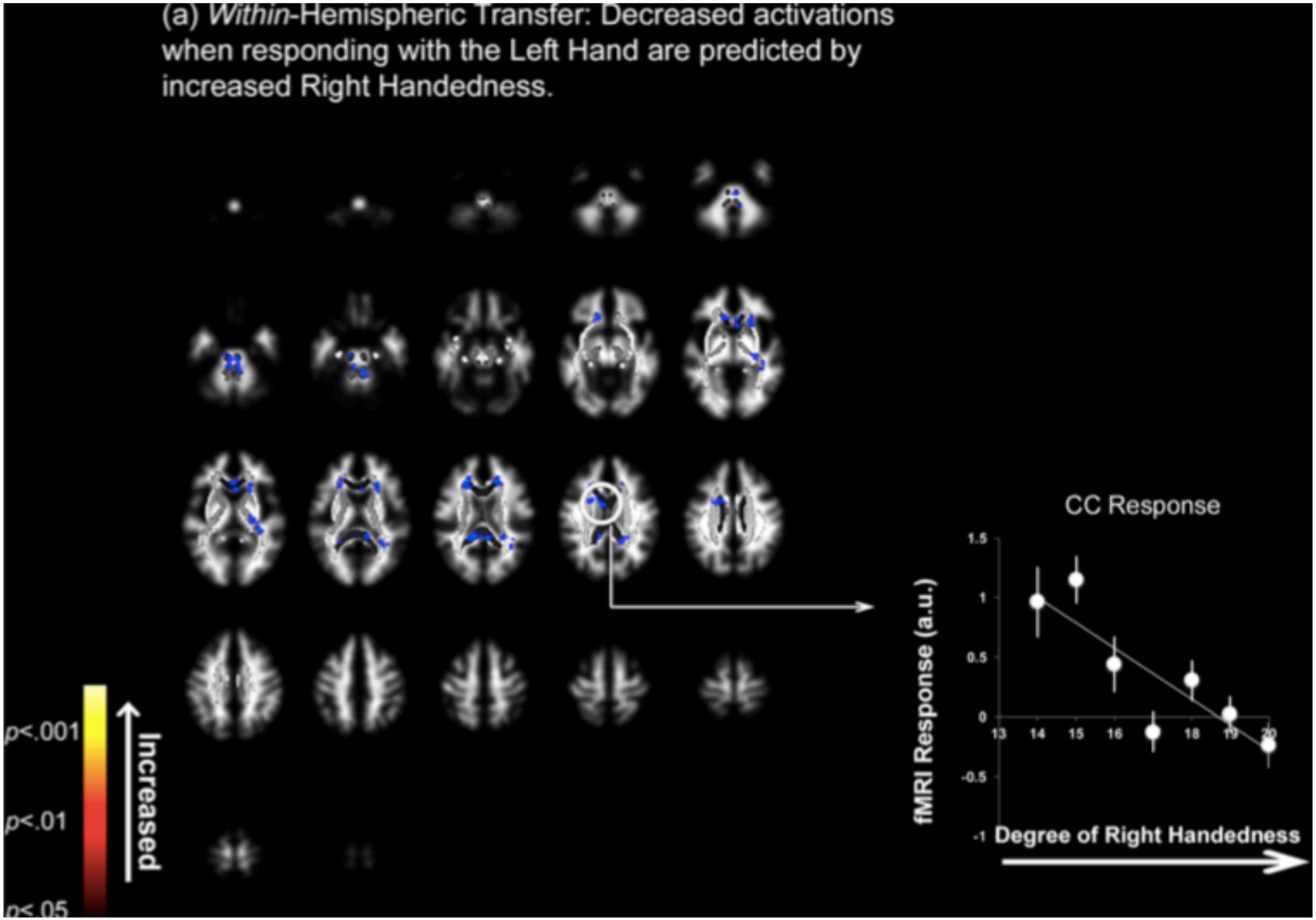


Diwadkar et al. (2018)



Tettamanti et al. (2002)

Historical observation of BOLD in WM



Diwadkar et al. (2018)

Observation & debate

« a reasonable investigator may doubt the presence of a BOLD signal in white matter altogether. »

Logothetis & Wandell
Interpreting the BOLD signal
Annu. Rev. Physiol. (2004)

« we are reluctant to interpret activations in white matter and will focus on discussing gray matter activations only. »

Weis et al.
Functional Neuroanatomy of Sustained Memory Encoding Performance in Healthy Aging and in Alzheimer's Disease
International Journal of Neuroscience **(2011)**

Observation & debate

« *However, evidence has emerged that CSF and WM compartments also contain fluctuations related to neural activity (Gawryluk et al., 2014; Renvall et al., 2014), especially when using scanners with stronger magnetic induction (Mazerolle et al., 2013).* »

Evaluation of different cerebrospinal fluid and white matter fMRI filtering strategies—Quantifying noise removal and neural signal preservation
Barton et al. *Hum Brain Mapp.* (**2018**)

=> Acknowledgement of white matter BOLD activation but removal nonetheless!

Observation & debate

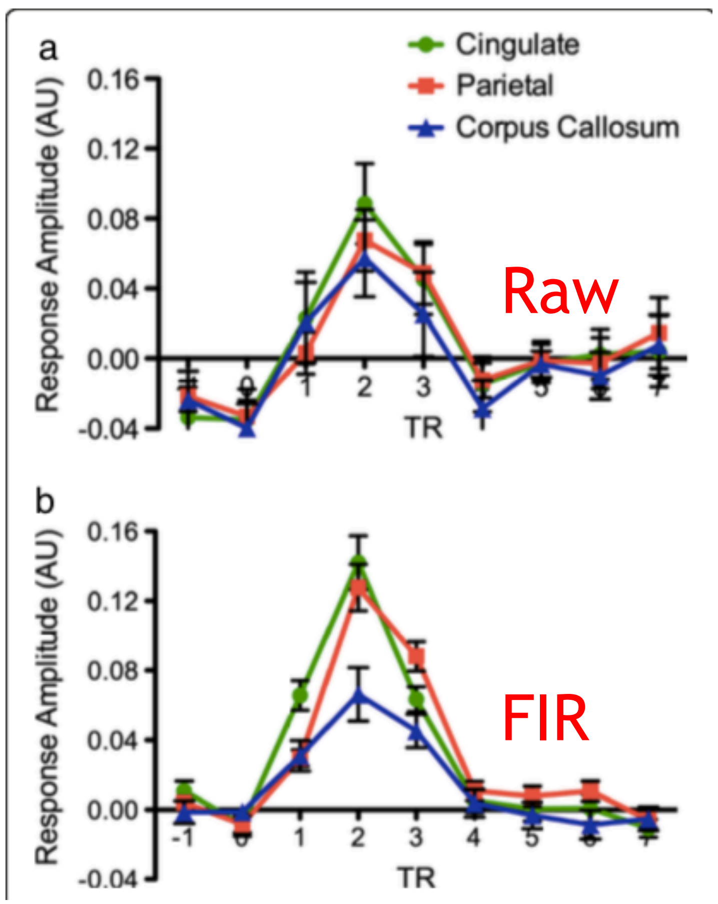
Evidence of Underreporting of White Matter FMRI Activation
Mazerolle et al. *J Magn Reson Imaging* (**2020**)

White Matter FMRI Activation Cannot Be Treated as a Nuisance Regressor: Overcoming a Historical Blind Spot.
Grajauskas et al. *Front*. *Neurosci*. (**2019**)

Does Functional MRI Detect Activation in White Matter? A Review of Emerging Evidence, Issues, and Future Directions.
Gawryluk, et la. *Front*. *Neurosci*. (**2014**)

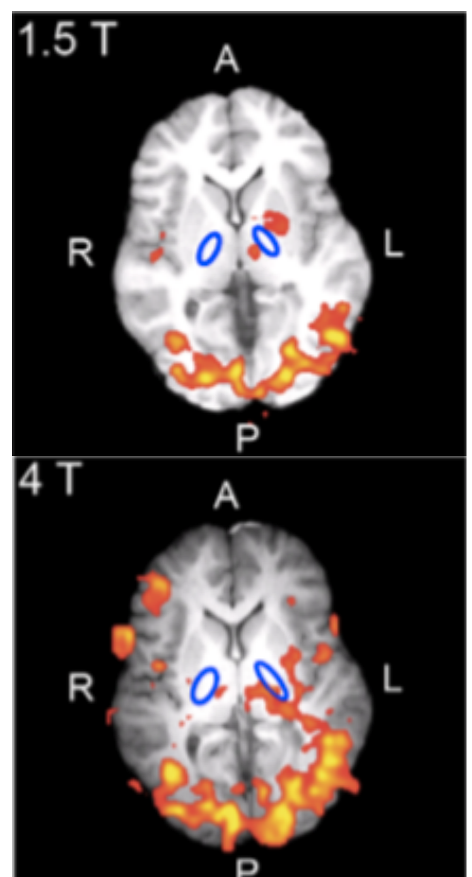
On going characterization of WM activation

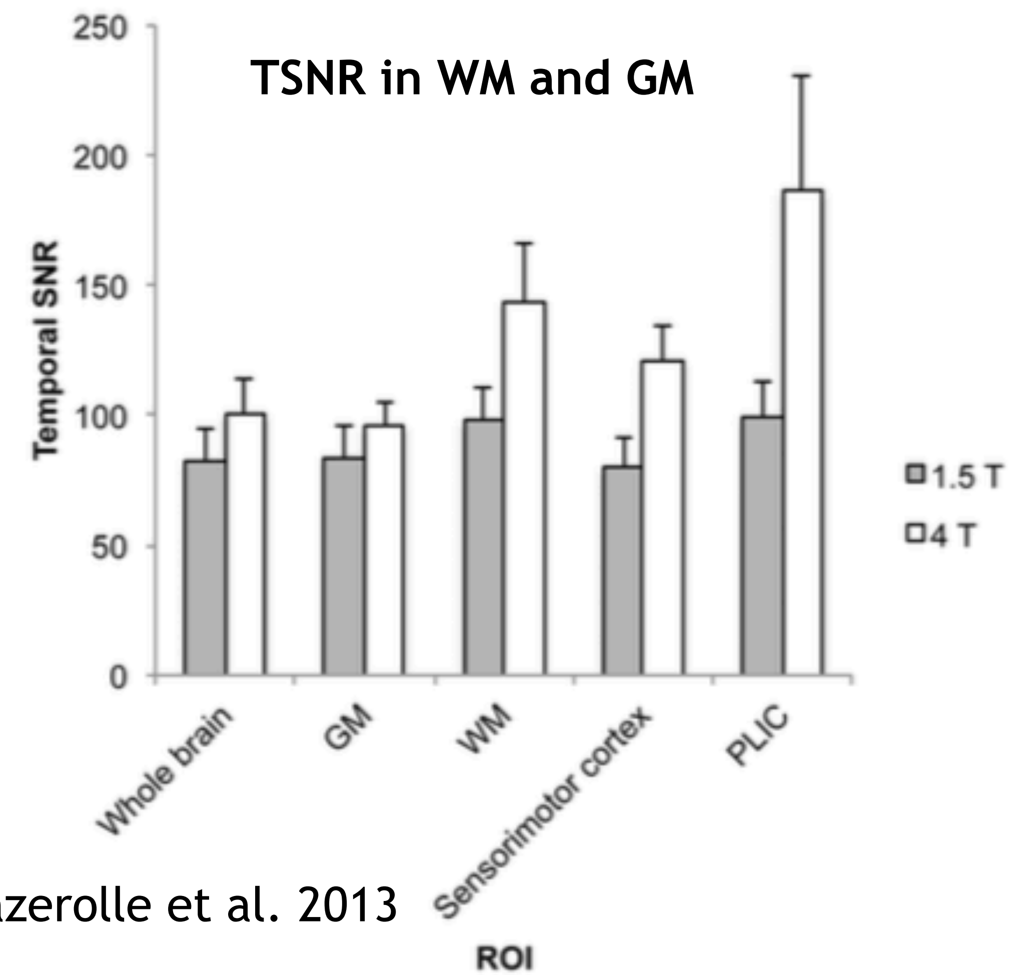
- Addition of DTI to evaluate whether regions of white matter fMRI activation have structural connections to activated gray matter.
- Callosal HRFs were compared to HRFs from cingulate and parietal activation.
- Specific Spin-echo Asymetric Spiral sequence is used to increase sensitivity to WM BOLD activation.



Fraser et al. 2012

- Sensitivity to WM BOLD activation increases with Field strength
- Physiological noise comprises a smaller proportion of the total noise in white matter compared to gray matter





Mazerolle et al. 2013

Assumed physiological origin of BOLD

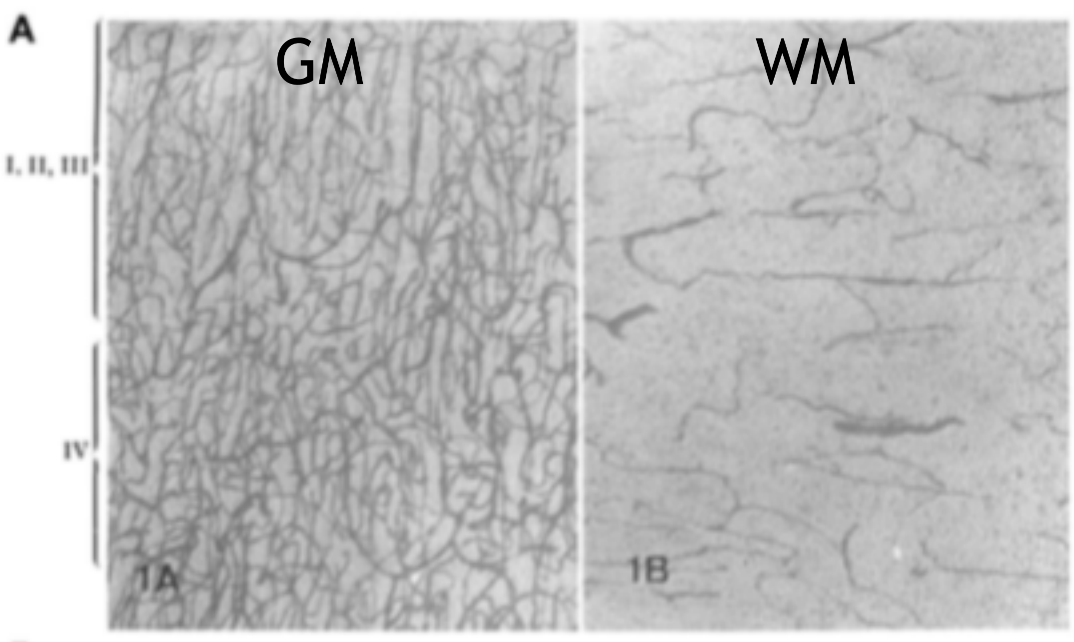
- BOLD contrast is highly dependent on cerebral blood flow (CBF) and volume (CBV)

=> Ratio for WM/GM: CBV: 1/3 ; CBF: 1/6

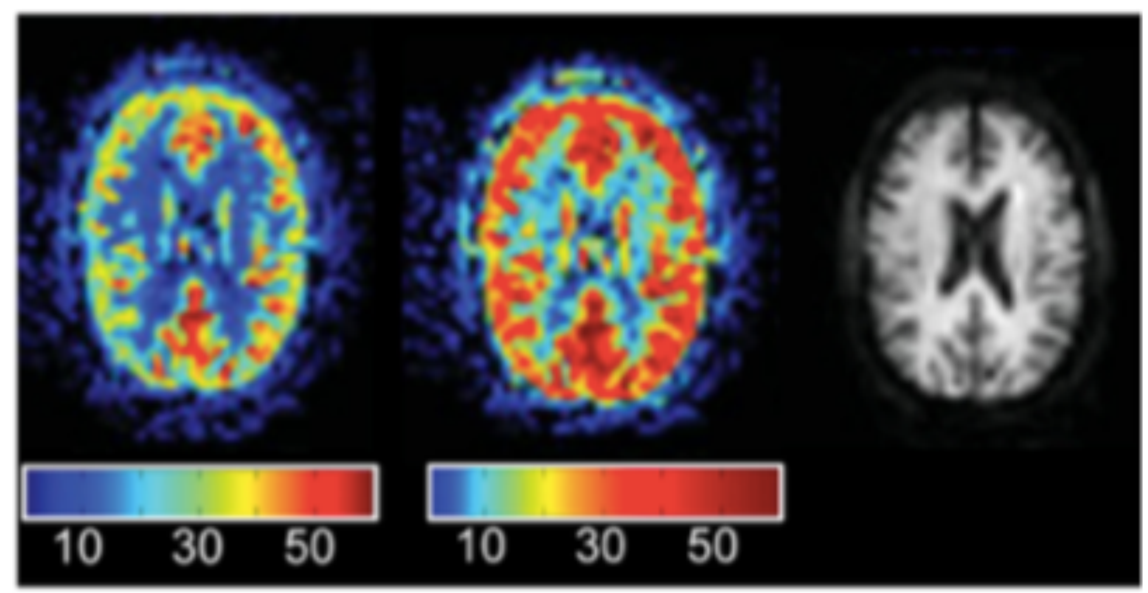
- There is evidence that local field potentials (which reflect post-synaptic potentials) are more closely linked to changes in BOLD-fMRI than multi-unit activity (which reflect action potentials) (Logothetis 2001)

=> source of the fMRI signal is thought to arise primarily from post-synaptic potentials rather than action potentials.

Vasculature



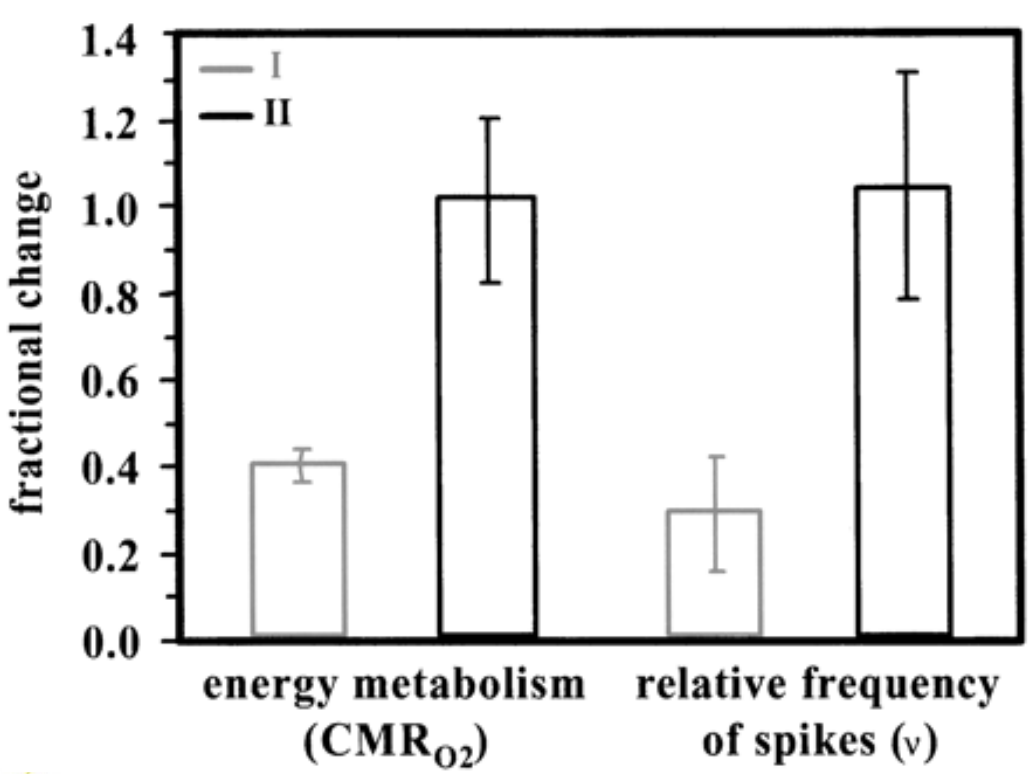
Perfusion (ASL)

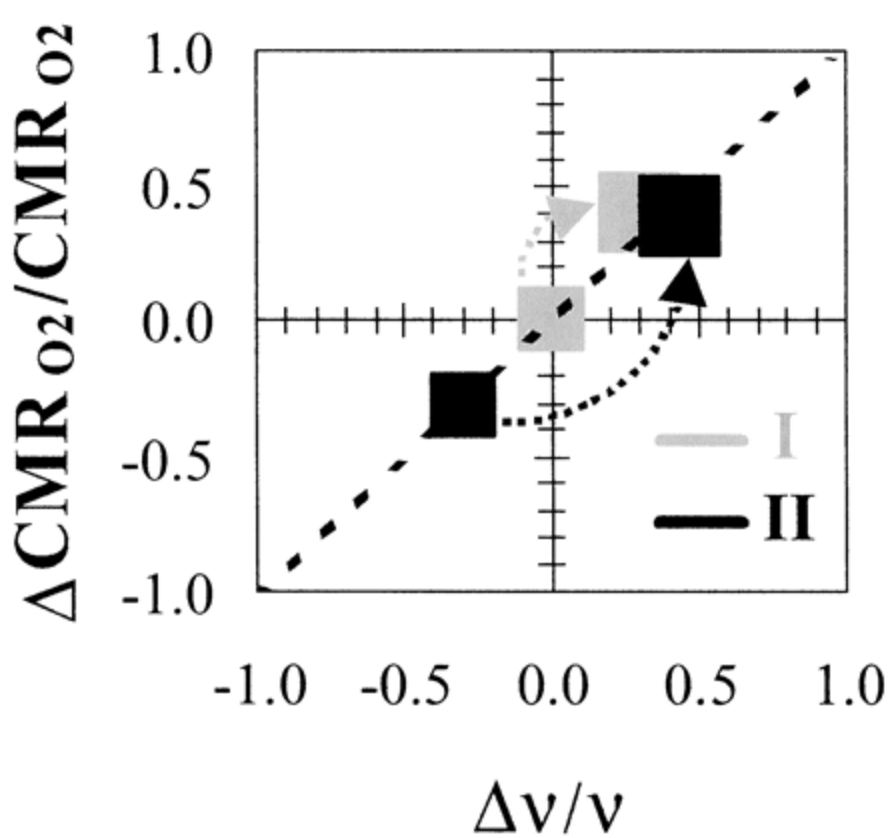


Assumed physiological origin of BOLD

- A relationship between spiking (which require energetic demands) and fMRI activation has also been reported.

E.g. : (Smith et al., 2002) : anesthetized rats (MRI at 7T & extracellular recordings) Changes in CMRO2 were calculated from the BOLD signal which required multimodal MRI measurements of changes in cerebral blood flow (ΔCBF/CBF), cerebral blood volume (ΔCBV/CBV), and BOLD signal (ΔS/S). ΔCBF/CBF (spin labeling) and ΔS/S (gradient and spin echo) were measured in an interleaved manner





Assumed physiological origin of BOLD

- But Harris and Attwell (2012) have proposed an energy budget for white matter, in which they estimate that the energy associated with spiking in white matter comprises only 0.4–7% of the total energy demand in white matter (depending on myelination status).

- Further food for thought :
  - Astrocytes' activity & K+ siphoning ?
  - NO (Nitric Oxide which is a powerful vasodilator) positive neurons transduce neuronal signals into vascular responses in selected [callosal] regions, thus giving rise to hemodynamic changes detectable by neuroimaging.

Table 1 | Factors that influence the ability to detect fMRI activation and how they differ across tissue types.

	Gray matter	White matter	Predicted effect on fMRI activation
Cerebral blood flow (CBF)	50–100 ml/100 g/min (Rostrup et al., 2000; Preibisch and Haase, 2001; Helenius et al., 2003)	10–30 ml/100 g/min (Rostrup et al., 2000; Helenius et al., 2003; Preibisch and Haase, 2001)	Reduced maximal amplitude of fMRI responses in white matter.
Cerebral blood volume (CBV)	4.6 ml/100 g (Helenius et al., 2003) 1.0–3.3% capillaries by volume (Lierse and Horstmann, 1965)	1.3 ml/100 g (Helenius et al., 2003) 0.3–0.9% capillaries by volume (Lierse and Horstmann, 1965)	Reduced maximal amplitude of fMRI responses in white matter.
Venous vessel size	13.4 micron radius (Jochimsen et al., 2010) 10–63 micron radius (intracortical veins; Duvernoy et al., 1981)	13.7 micron radius (Jochimsen et al., 2010) 30–60 micron radius (Duvernoy et al., 1981)	If the vessels in white matter are of equal or greater size than those in gray matter, one might expect a tendency toward greater sensitivity in white matter for standard gradient-echo BOLD sequences (Boxerman et al., 1995). However, it is likely that the effect of lower CBF and CBV in white matter is the dominant factor, consistent with the notion of reduced sensitivity to activation in white matter.
T2*	89.3 ms (1.5 T) 59.7 ms (3 T) N.B. Values for cortical gray matter (Peters et al., 2006)	71.7 ms (1.5 T) 54.6 ms (3 T) (Peters et al., 2006)	Optimal TE depends on T2*; standard fMRI parameters may not be optimized for detecting white matter activation, particularly at 1.5 T due to greater differences between the tissue types.
Physiological noise	Higher (Bodurka et al., 2007)	Lower (Bodurka et al., 2007)	White matter fMRI signals may be less contaminated by physiological noise than gray matter.

Gawryluk et al. - 2014 - fMRI White Matter Review

Table 1 | Factors that influence the ability to detect fMRI activation and how they differ across tissue types.

	Gray matter	White matter	Predicted effect on fMRI activation
Tissue geometry	Cortical gray matter has substantial potential for PVE with CSF in sulci	Some areas of white matter are very uniform; others neighbor gray matter and/or the lateral ventricles	PVEs are problematic throughout white and gray matter.
Categories of neural activity	Post-synaptic potentials and action potentials	Mostly action potentials	Both are linked to BOLD fMRI signal changes (e.g., Logothetis et al., 2001; Smith et al., 2002).
Presence of activity-dependent metabolic changes	Observed using numerous techniques, including calibrated fMRI (Hoge et al., 1999), PET (Magistretti, 2006), and optical imaging (Devor et al., 2012)	Observed using autoradiology (Weber et al., 2002)	While white matter supports activity-dependent metabolic changes, the autoradiography evidence does not provide sufficient temporal resolution to imply that such changes might be detectable with BOLD fMRI.
Astrocytes	Positioned to facilitate neurovascular coupling (Petzold and Murthy, 2011)	Positioned to facilitate neurovascular coupling (Petzold and Murthy, 2011)	Underlying neurophysiology of gray and white matter fMRI activation may share overlapping components.

Gawryluk et al. - 2014 - fMRI White Matter Review

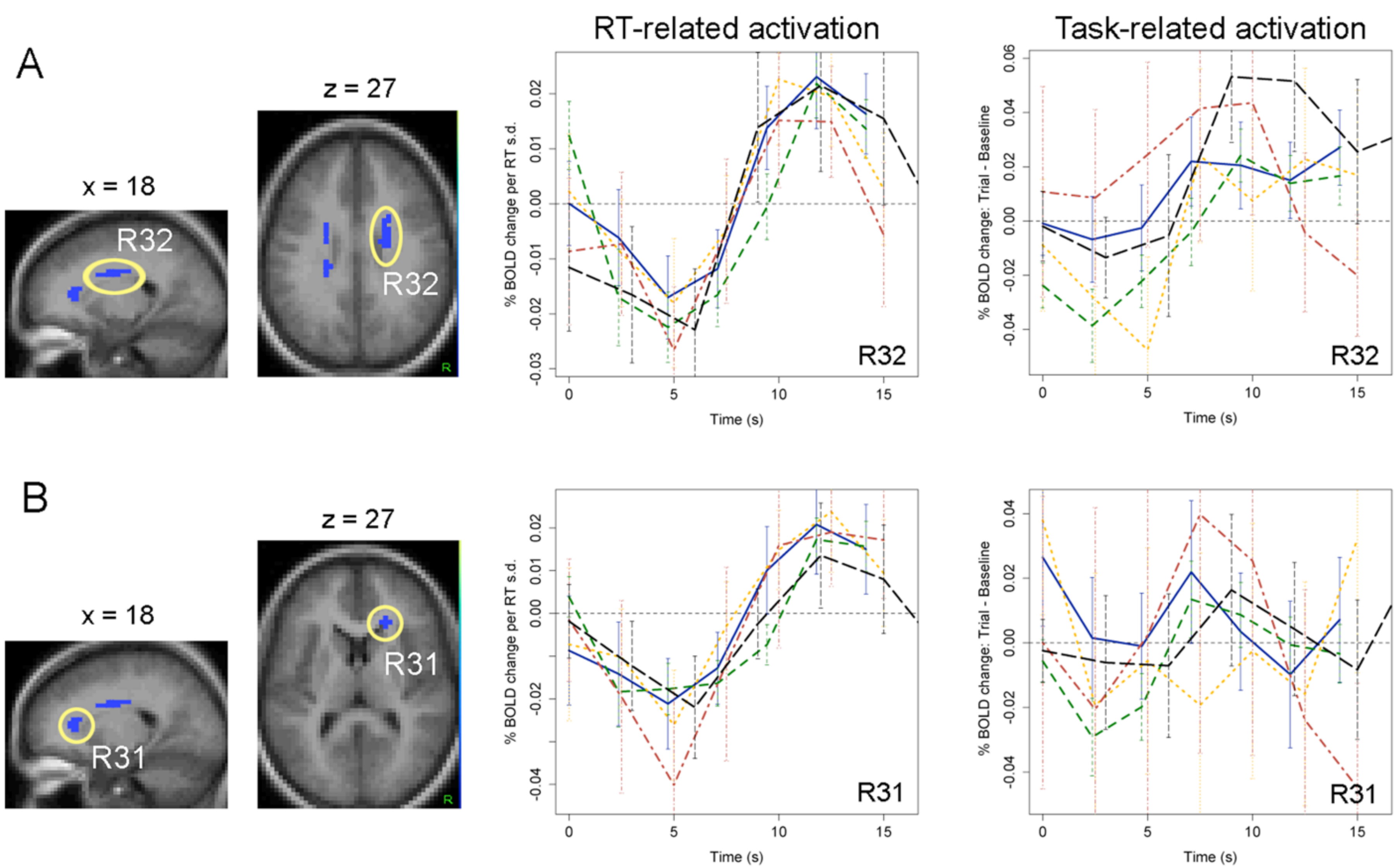
Biases in fMRI research towards Grey Matter

- Exploration / optimisation of the TE (because the T2 and T2∗ are different between white and gray matter)

  Nota : at 3T, we often use a TE ≈ 30 ms which seems to be at least as optimal for WM (T2* ≈ 55ms) than for GM (T2* ≈ 60ms)

Biases in fMRI research towards Grey Matter

- The shape of the HRF is assumed (the famous canonical one) although it is known to differ between brain regions and between GM & WM



Yarkoni & al, 2009

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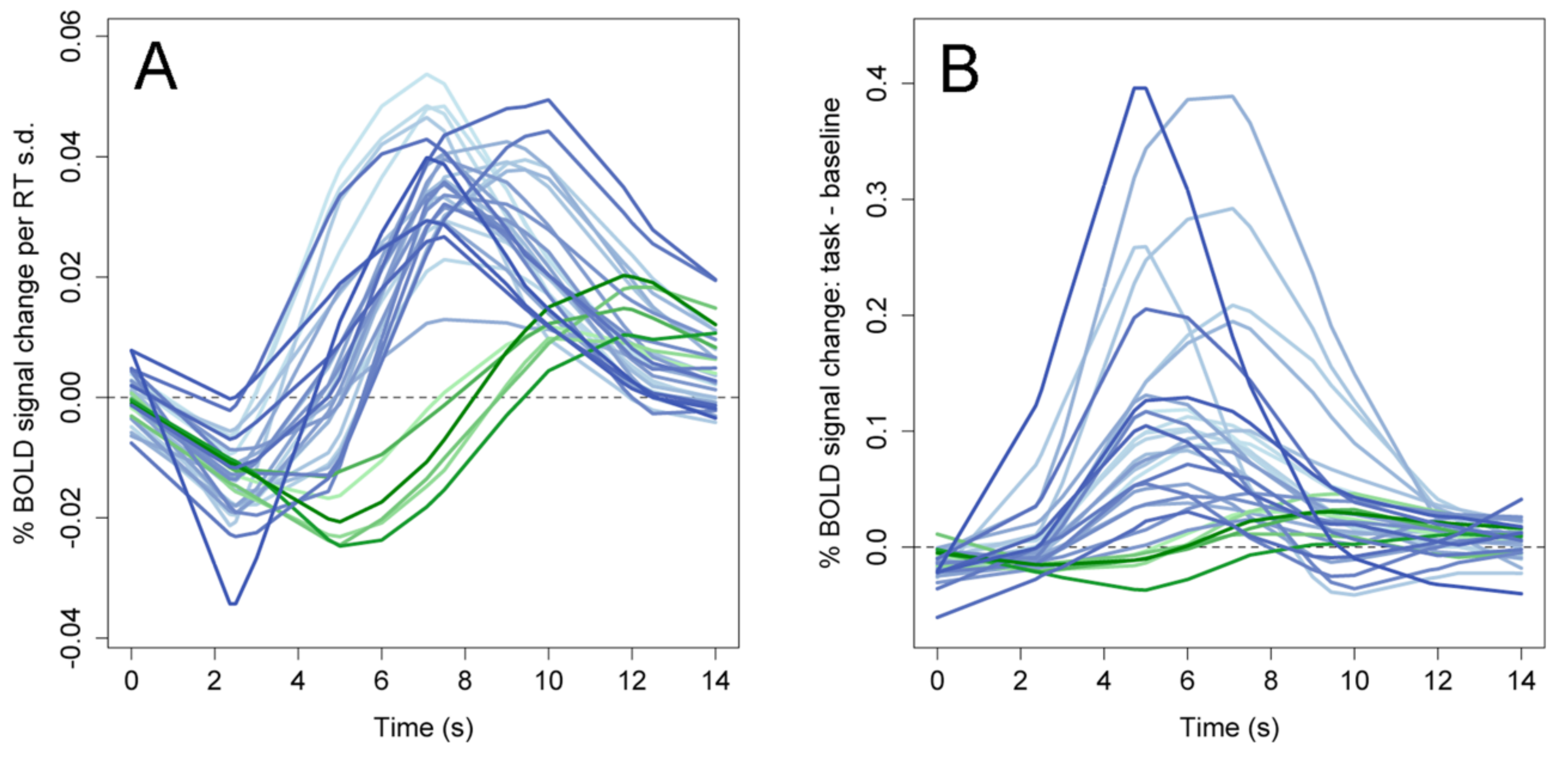


Each time course represents the time course of Reaction Time -related activation (A) or task-related activation (B) in a single region. Blue: gray matter ROIs; green: white matter ROIs.

Yarkoni & al, 2009

Biases in fMRI research towards Grey Matter

- The common use of white matter signals as a nuisance regressor !

  → This approach is sensible if and only if :

  1/ there are no signals of interest in white matter : this is the question !

  2/white matter is more prone to artifacts than gray matter
  - yet, WM less sensitive to head motion (less boundary)
  - yet, WM less sensitive to spin history effects (less susceptibility field gradients)
  - partial volume effect (with the GM) : use of conservative masks

Yarkoni & al, 2009

Biases in fMRI research towards Grey Matter

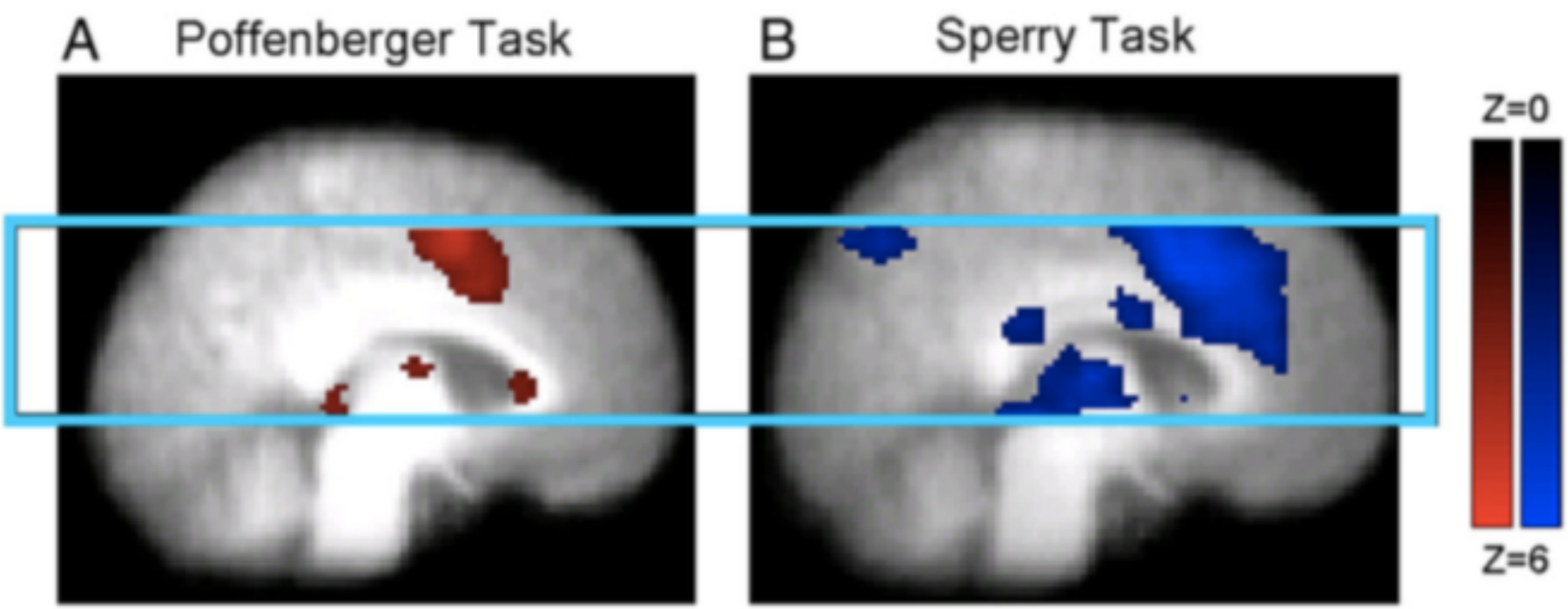
- Let's look further and elsewhere ...

  Poline et al. (2006): "neuroscientists or clinicians [typically] assess [fMRI] results in relation to their prior expectations, although this biases fMRI studies away from making new and unexpected discoveries"

Some White Matter fMRI studies …

- A lot of studies from the group of Ryan C.N. D'Arcy (Halifax, Canada)

  Gawryluk et al (2011) Functional mapping in the corpus callosum : A 4 T fMRI study of white matter

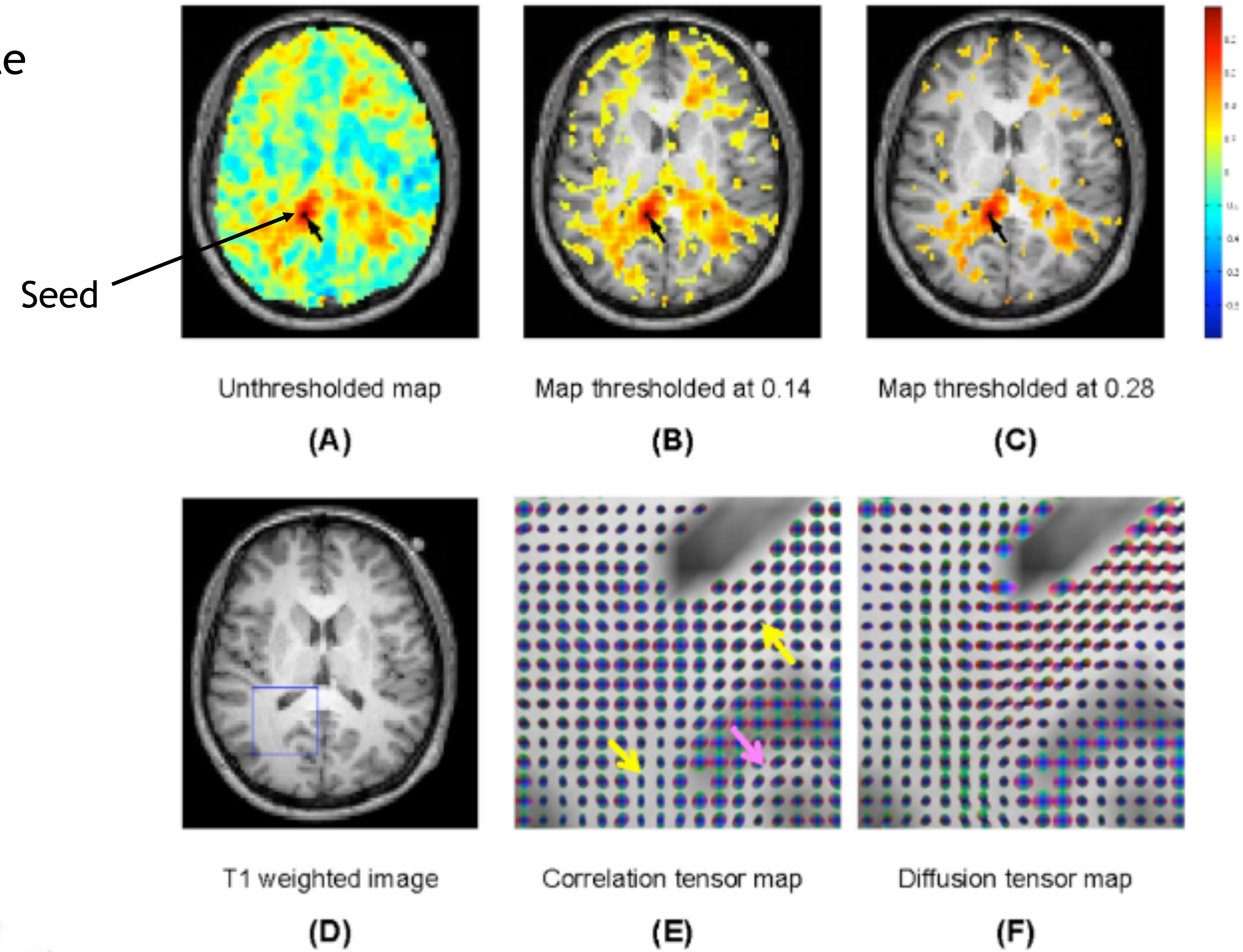


- Interhemispheric transfer activation

Some White Matter fMRI studies …

- Group of John C. Gore : Ding & al (2013) « Spatio-Temporal Correlation Tensors Reveal Functional Structure in Human Brain »

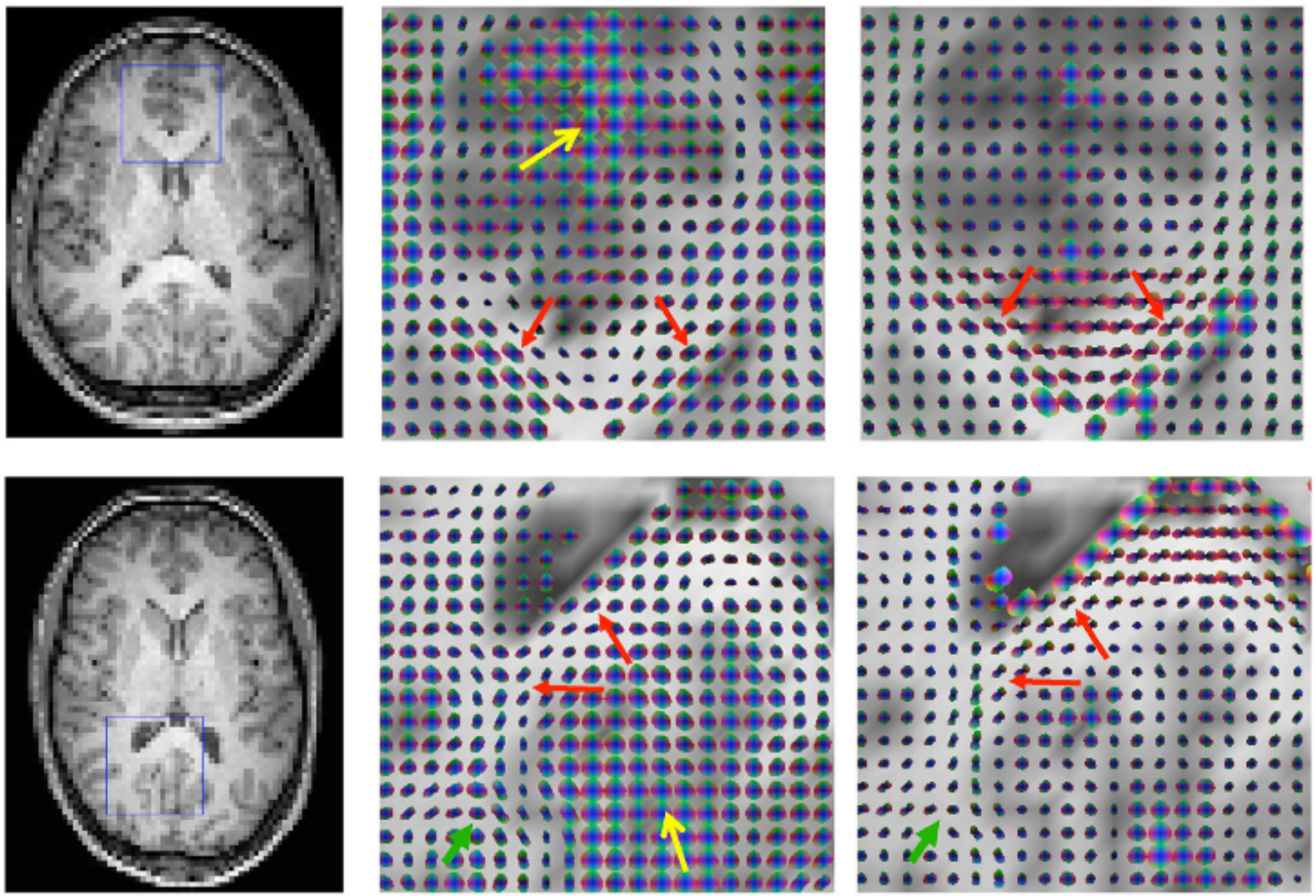
Resting State



Some White Matter fMRI studies …

- Gore's group : Ding & al (2016) « Visualizing functional pathways in the human brain using correlation tensors and MRI »

Resting State



Genu of the corpus callosum

Splenium of the corpus callosum

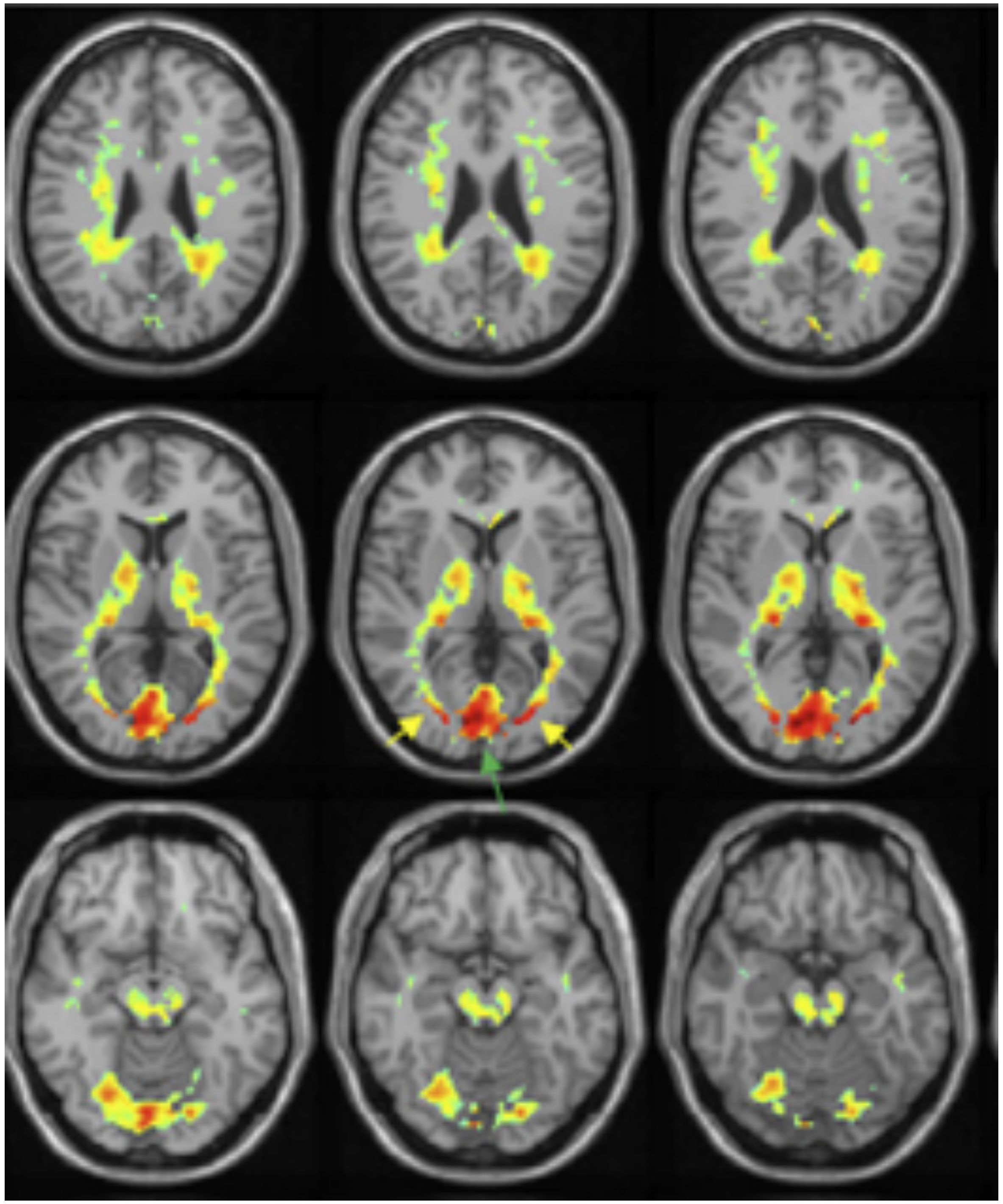
Spatio-temporal functional correlation tensors (FCTs)

Diffusion tensors

Some White Matter fMRI studies …

- Gore's group : Huang & al (2018) « Voxel-wise detection of functional networks in white matter »

Visual stimulation



CV = the standard deviation divided by the mean

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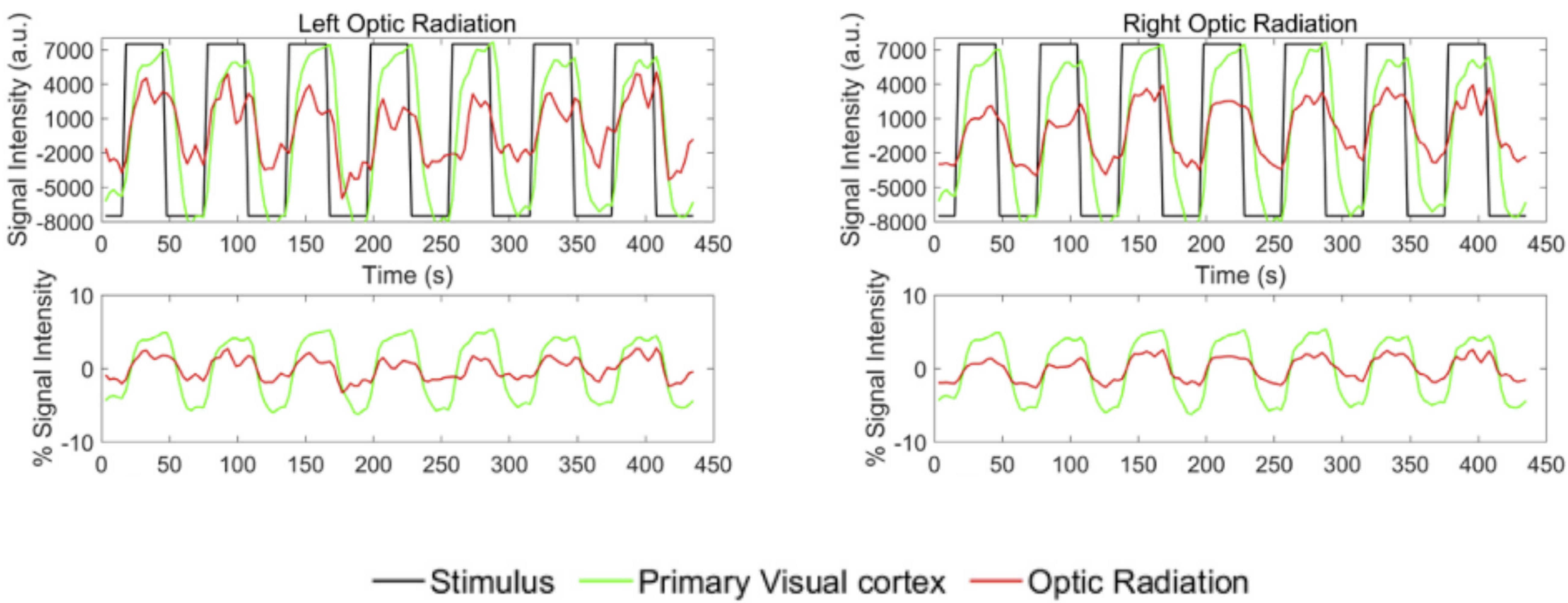
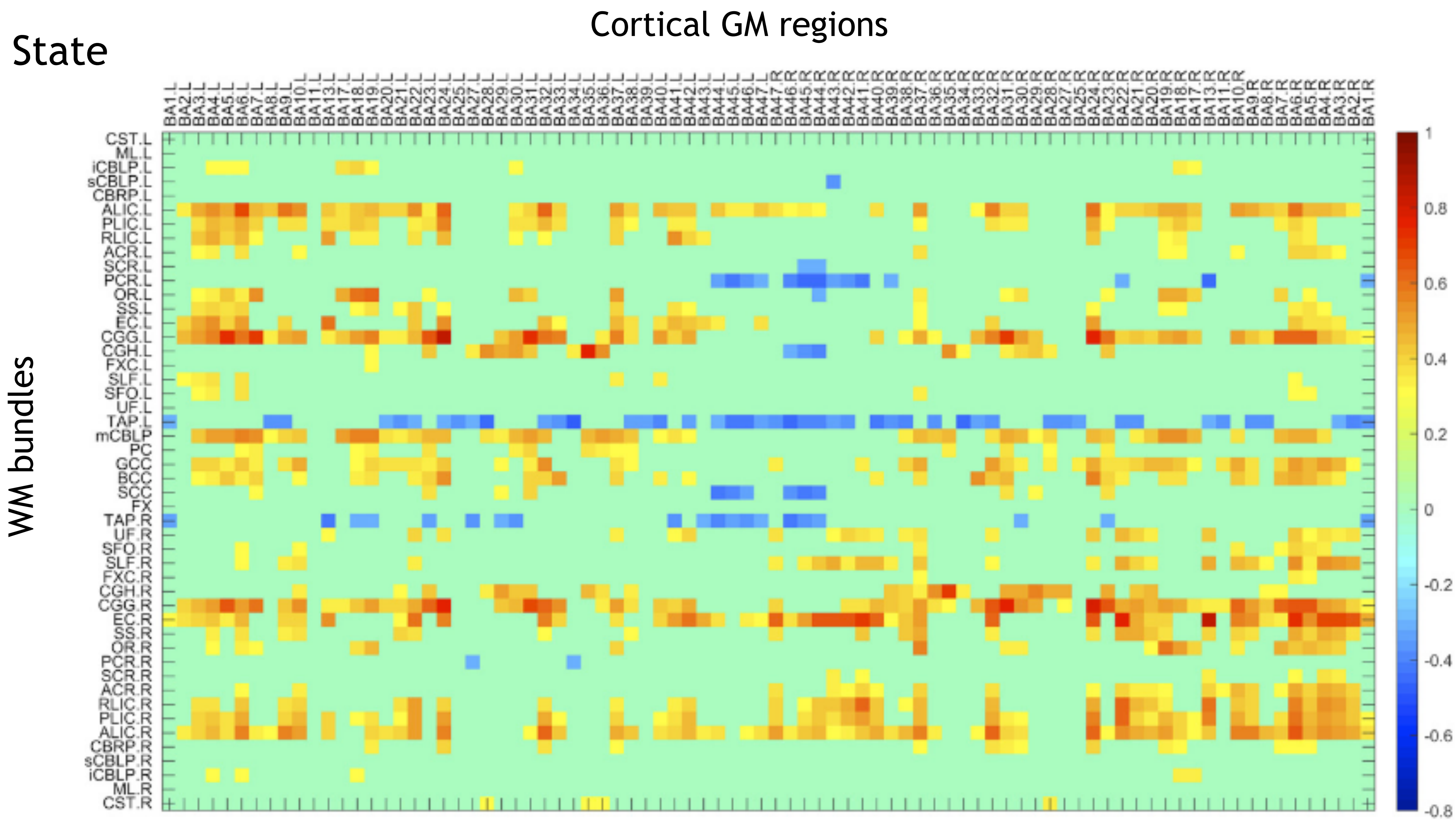


Some White Matter fMRI studies …

- Gore's group : Ding & al (2018) « Detection of synchronous brain activity in white mattertracts at rest and under functional loading »

Resting State



Some White Matter fMRI studies …

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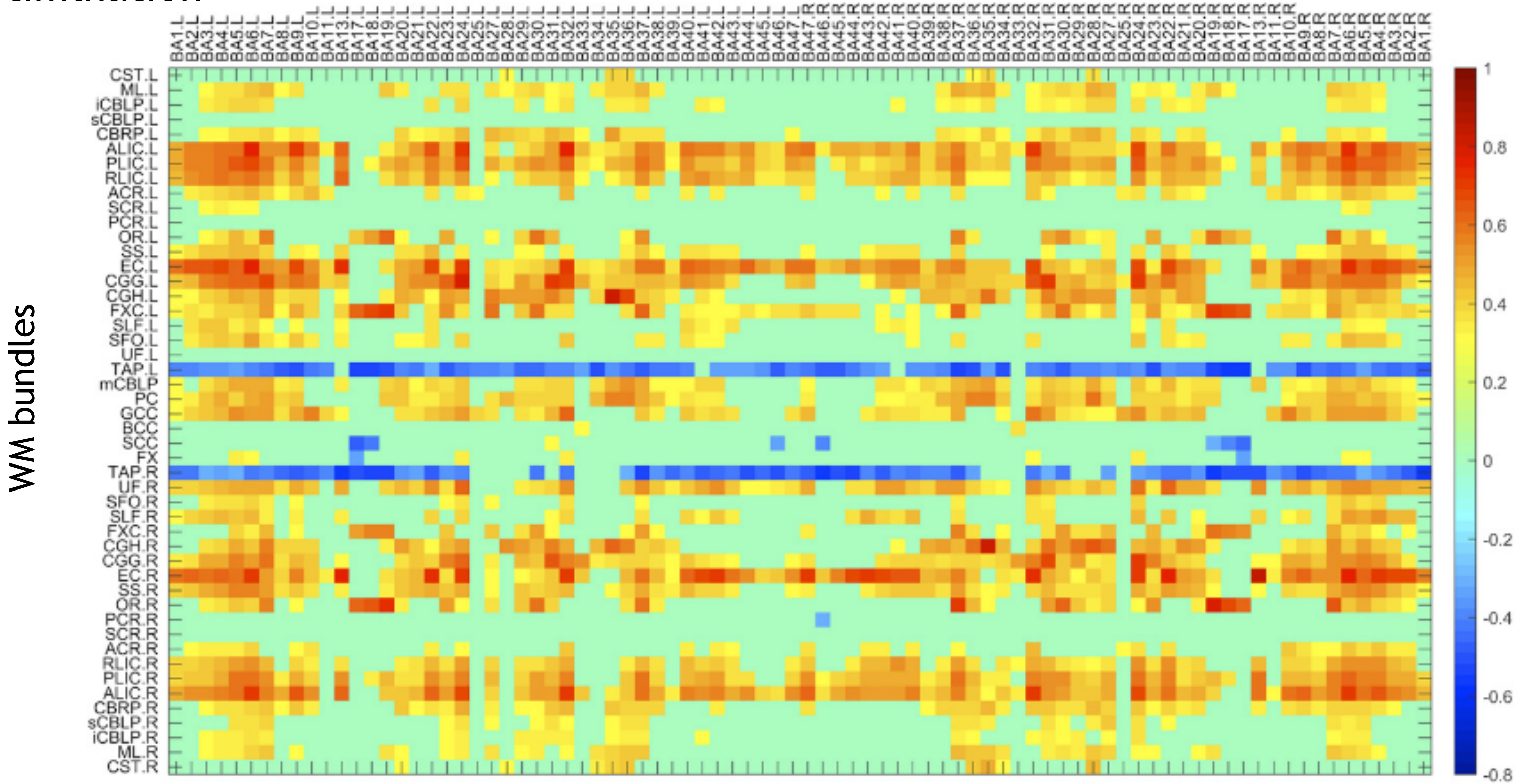
Visual stimulation

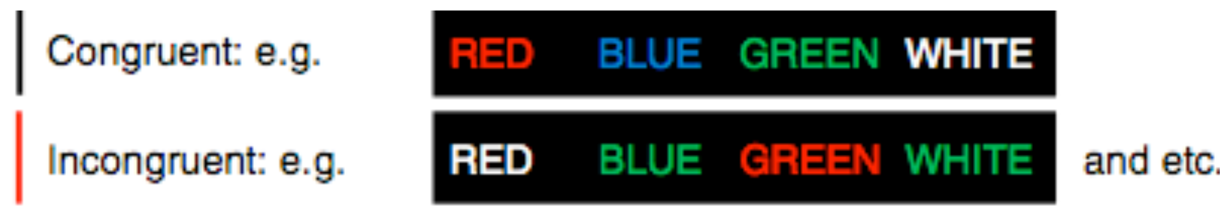
Cortical GM regions

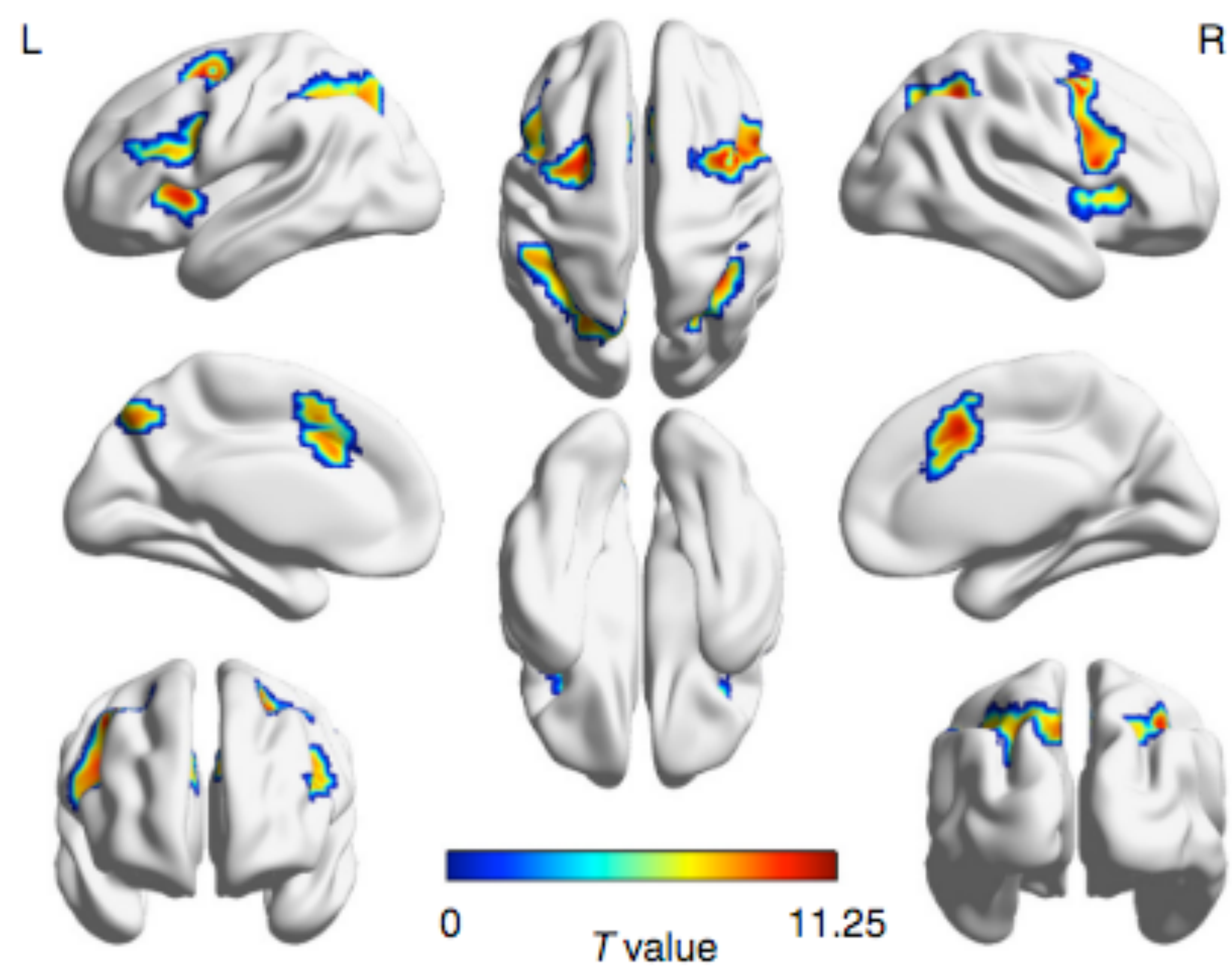


Some White Matter fMRI studies …

- Gore's group : Li & al (2019) Characterization of the HRF in white matter tracts for event-related fMRI

Stroop word-color task :
incongruent vs congruent

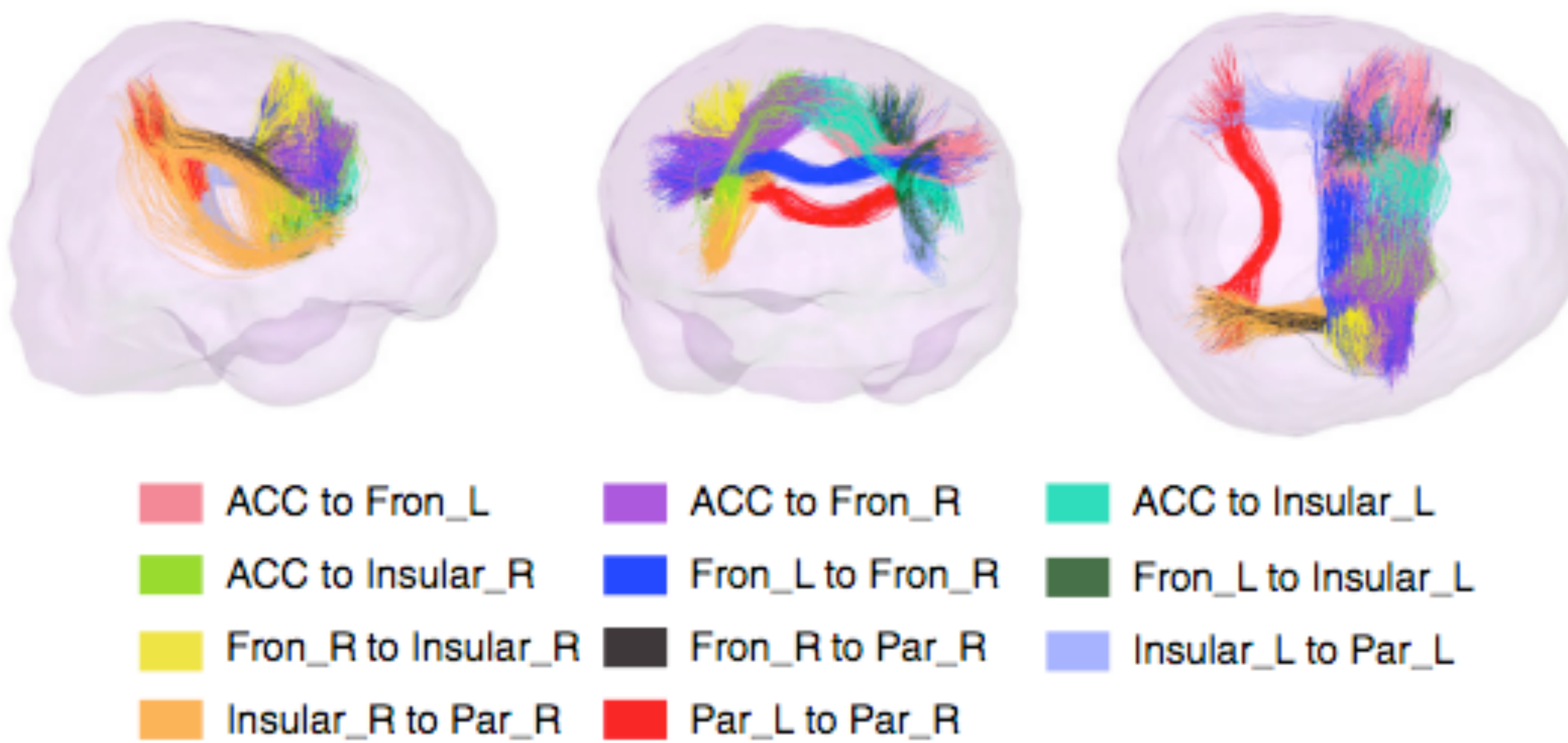




Some White Matter fMRI studies …

- Li & al (2019)

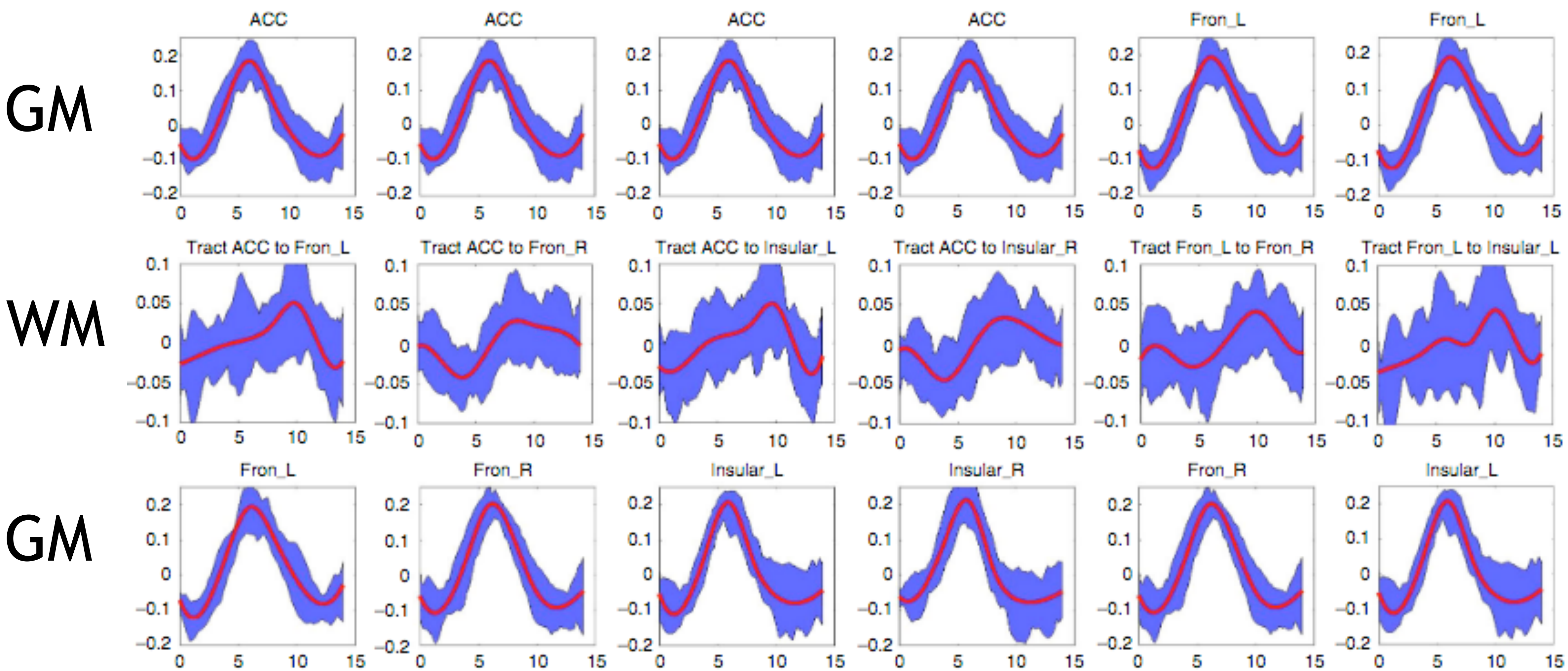
MRI diffusion tractography



Some White Matter fMRI studies …

- Li & al (2019)

Average time courses in WM tracts and their connecting GM clusters

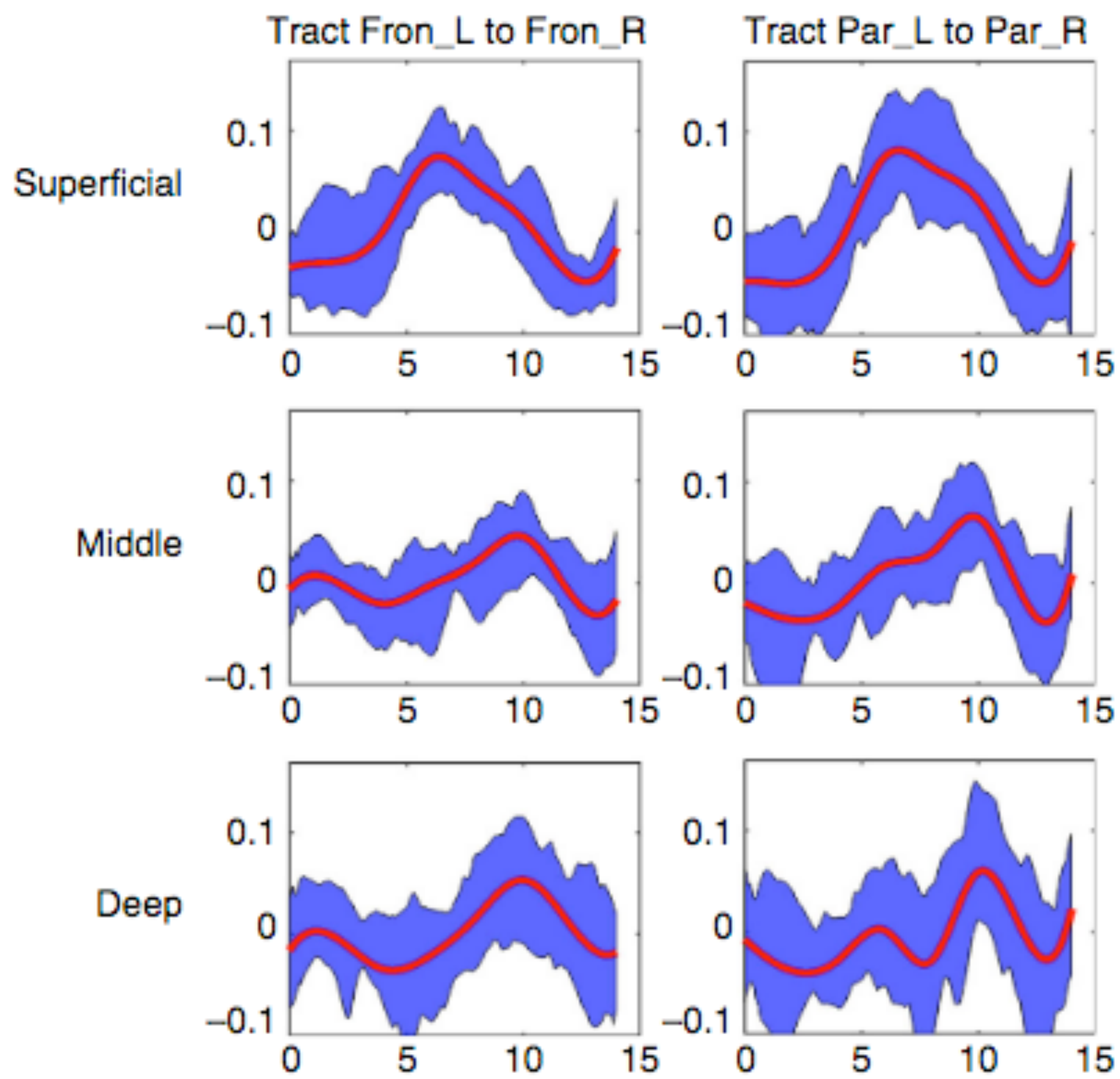


→ HRF in WM much smaller, delayed and variable than in GM

Some White Matter fMRI studies …

- Li & al (2019)

Average time courses in different depths of the WM tract



→ HRF in deep WM smaller, delayed and variable than in superficial WM (which looks more similar to that of GM)

Some White Matter fMRI studies …

- Li & al (2019)

GM and WM activations detected using GM and WM HRFs

GM canonical HRF

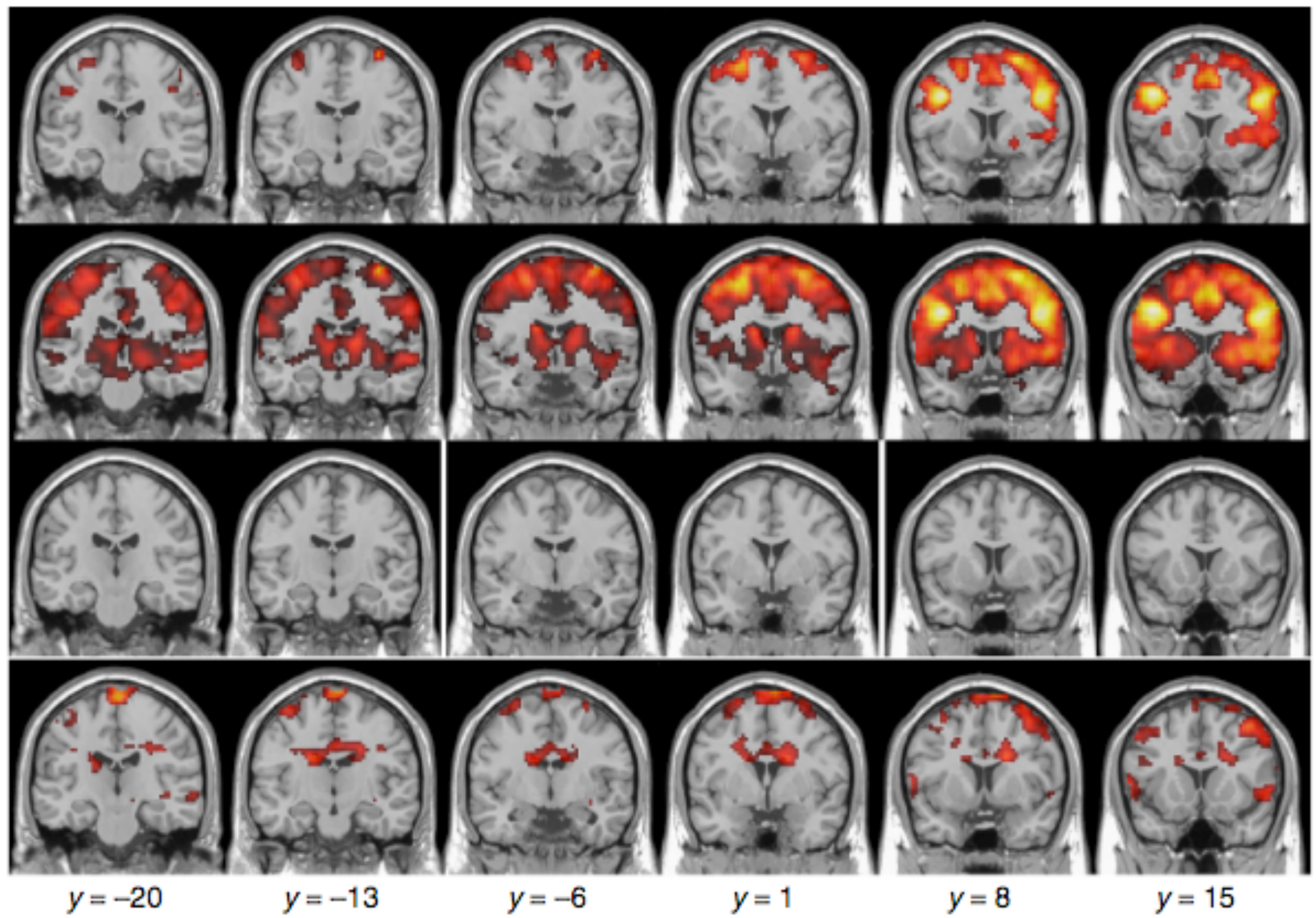
P< 0.05, FWE corrected

P< 0.02, uncorrected !!

WM custom regressor

P< 0.05, FWE corrected

P< 0.02, uncorrected !!



→ Weak activation that does not survive the usual statistical thresholds

Implications & conclusions

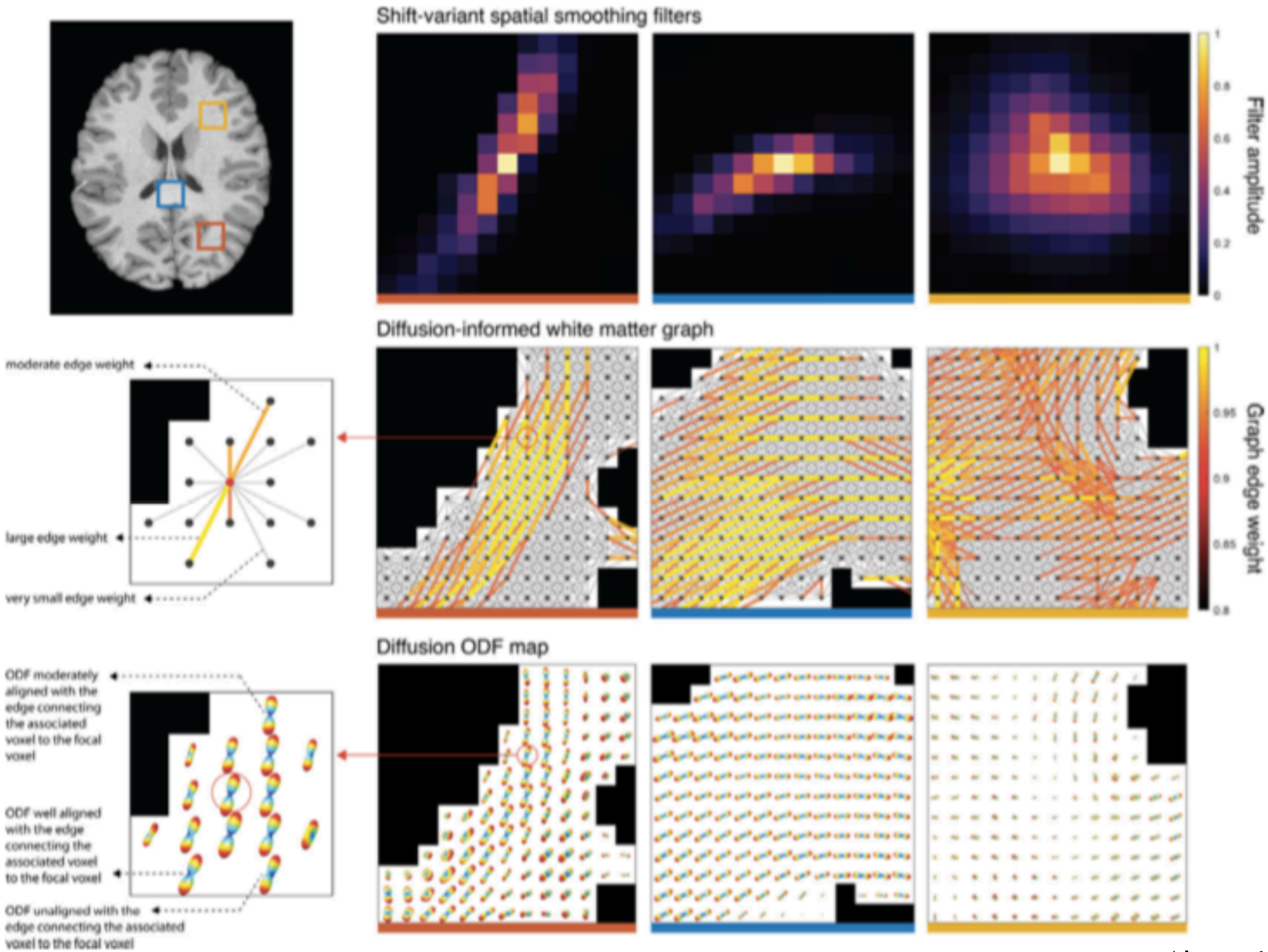
- Existence of a potential BOLD signal variation in the White Matter related to local brain activity …
  But it seems that only two research groups produce the majority of articles on white matter activation : John C. Gore & Ryan C.N. D'Arcy

- Be careful with the denoising approaches : not to aggressive
  - Check with and without WM signal regression-out (aCompCor with or without the WM as nuisance region)

- Watch with " kindness " the signal variations in the WM
  - Study their position in relation to the clusters that might be involved in cognitive processes (those linking two Grey Matter regions activated by the protocol)

- Use alternative adaptive smoothing approaches to incorporate information from the domain on which the data resides, typically provided by complementary anatomical images.
  Ex: Diffusion Informed spatial smooting: Abramian et al. NeuroImage (2021)

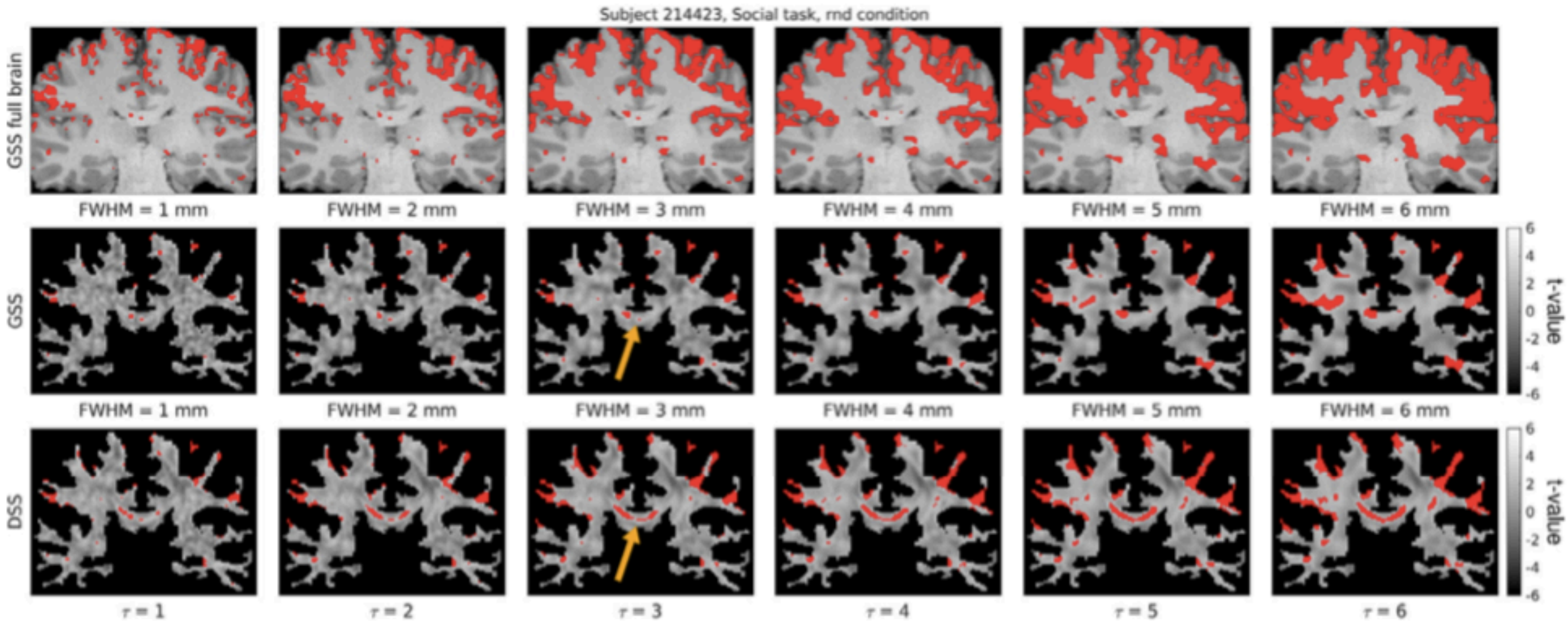
Implications & conclusions



Abramian et al. 2021

Generation of diffusion informed smoothing

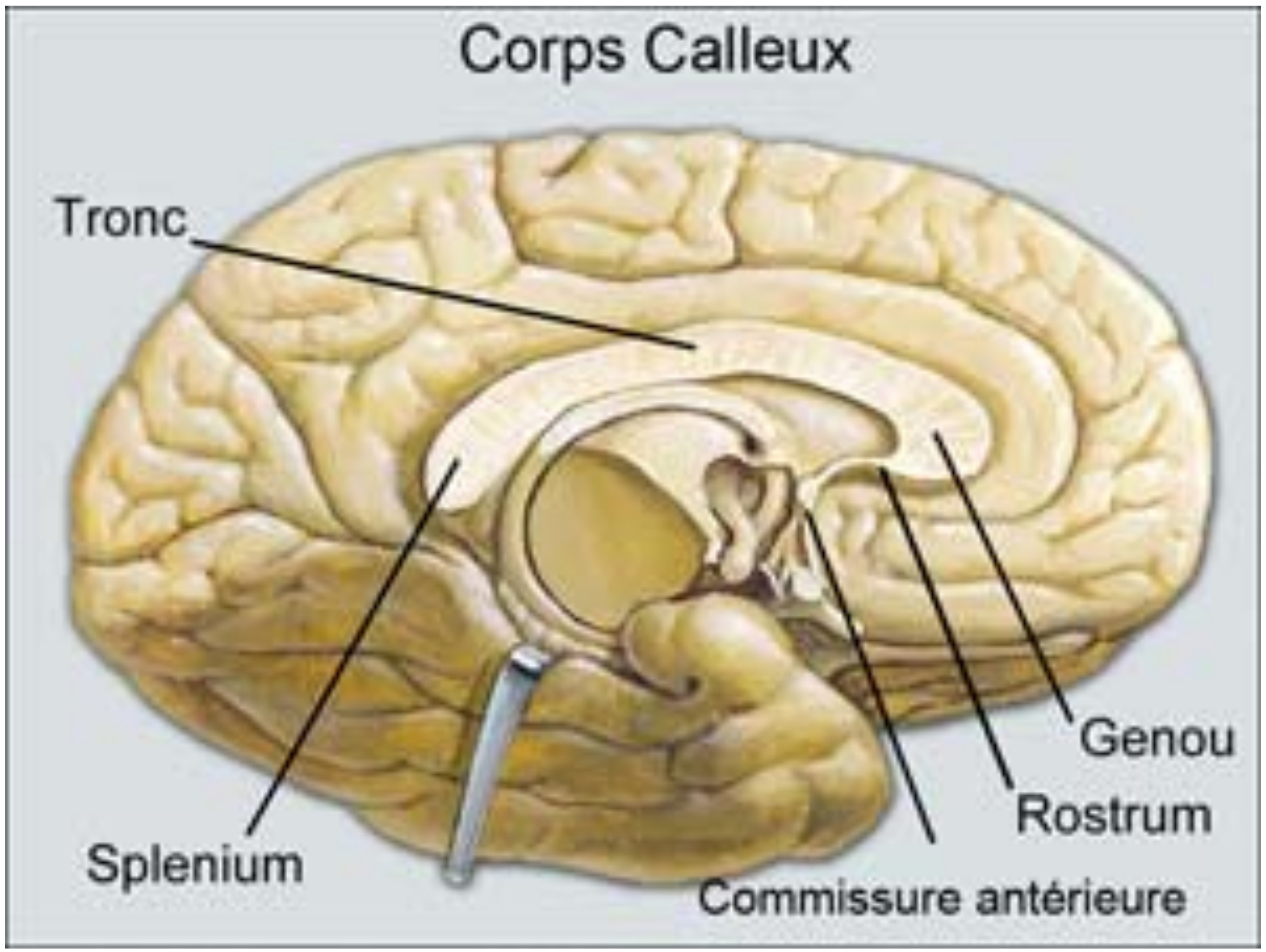
Implications & conclusions



Individual activation maps with Gaussian smoothing full brain, WM mask or via diffusion informed smoothing.
HCP data, t-maps, FDR corrected at 5%

Abramian et al. 2021

Thank you …


Corps Calleux
Tronc
Splenium
Genou
Rostrum
Commissure antérieure

Physiological basis of BOLD

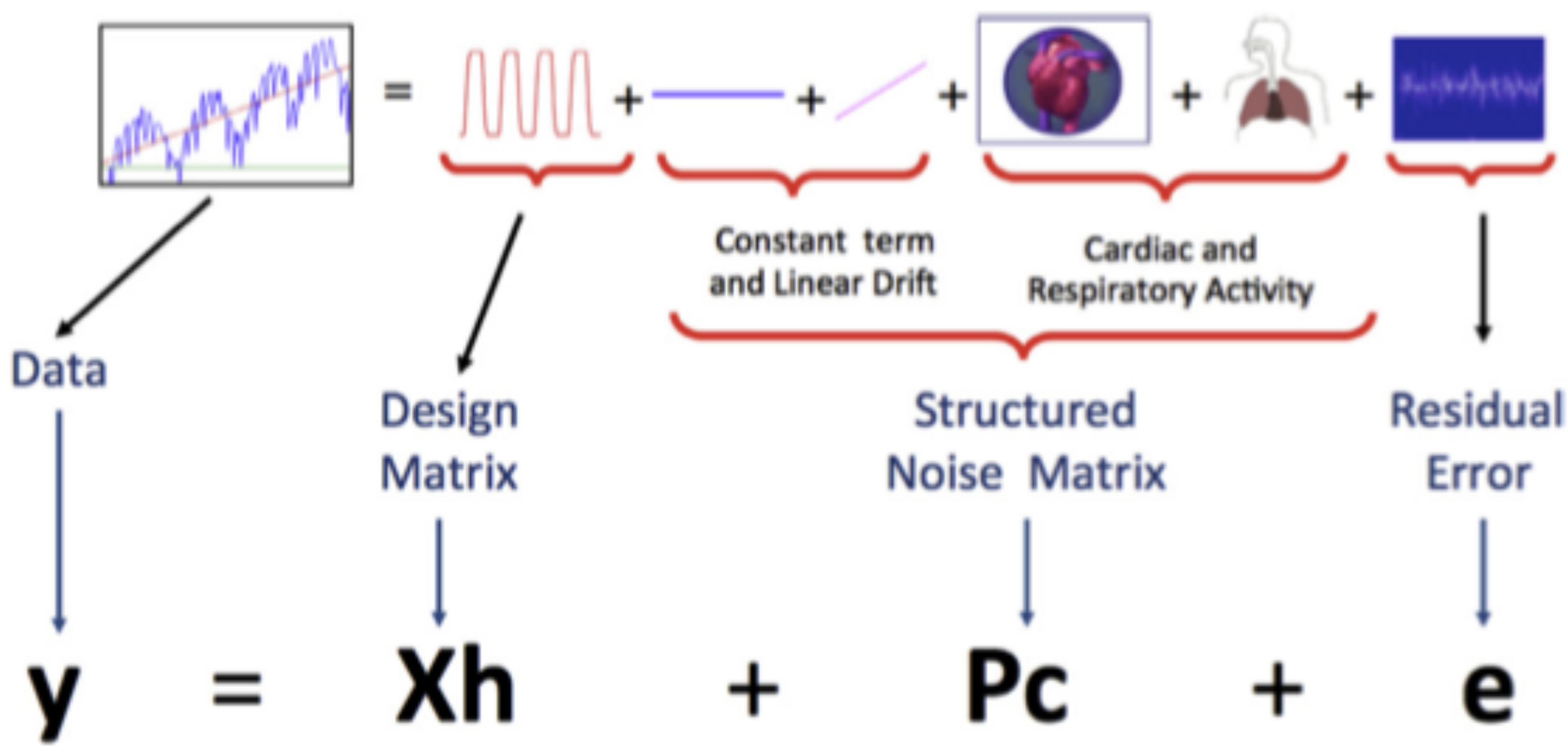
$$S(t) = S_0(t) \cdot \exp\left(- R_2^*(t) \cdot \mathrm{TE} \right) + n(t)$$

Non-Bold sensitive term

Bold sensitive term

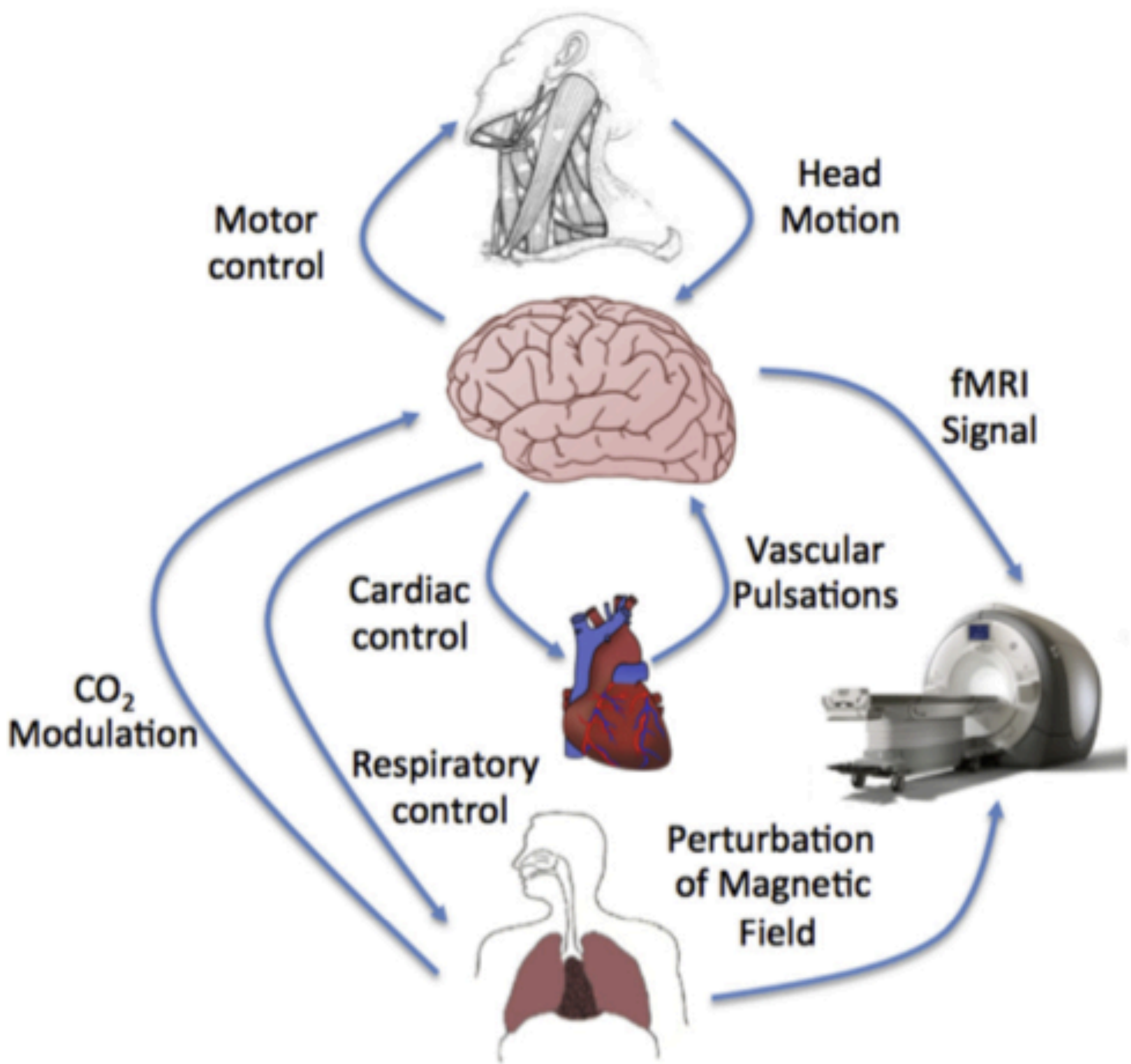
$$\frac{\Delta S(t)}{S(0)} \approx \frac{\Delta S_0(t)}{S_0(0)} - \mathrm{TE} \cdot \Delta R_2^*(t) + \frac{\Delta n(t)}{S(0)}$$

Background noise term



Liu et al. 2016

Physiological origin of noise in fMRI signal



Liu et al. 2016