

Hemodynamic Deconvolution Demystified: Sparsity-Driven Regularization at Work

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Abstract

Deconvolution of the hemodynamic response is an important step to access short timescales of brain activity recorded by functional magnetic resonance imaging (fMRI). Albeit conventional deconvolution algorithms have been around for a long time (e.g., Wiener deconvolution), recent state-of-the-art methods based on sparsity-pursuing regularization are attracting increasing interest to investigate brain dynamics and connectivity. This technical note revisits the main concepts underlying two main methods, Paradigm Free Mapping and Total Activation, in the most accessible way. Despite their apparent differences, these methods are theoretically equivalent as they represent the synthesis and analysis sides of the same problem. We demonstrate this equivalence in practice with their best-available implementations using both simulations, with different signal-to-noise ratios, and experimental data of motor task and resting-state fMRI. We evaluate the parameter settings that lead to equivalent results, and showcase the potential of these algorithms compared to other widely-used approaches. This note is useful for practitioners interested in gaining a better understanding of state-of-the-art hemodynamic deconvolution, and who want to make use of them with the most efficient implementation.

Keywords: fMRI deconvolution, paradigm free mapping, total activation, temporal regularization

1. Introduction

Functional magnetic resonance imaging (fMRI) data analysis is often directed to identify and disentangle the neural processes that occur in different brain regions during task or at rest. As the blood oxygenation level-dependent (BOLD) signal of fMRI is only a proxy for neuronal activity mediated through neurovascular coupling, an intermediate step that estimates the activity-inducing signal, at the timescale of fMRI, from the BOLD timeseries can be useful. Conventional analysis of task fMRI data relies on the general linear models (GLM) to establish statistical parametric maps of brain activity by regression of the empirical timecourses against hypothetical ones built from

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the knowledge of the experimental paradigm. However, timing information of the paradigm can be
10 unknown, inaccurate, or insufficient in some scenarios such as naturalistic stimuli, resting-state, or
clinically-relevant assessments.

Deconvolution and methods alike are aiming to estimate neuronal activity by undoing the blurring effect of the hemodynamic response, characterized as a hemodynamic response function (HRF). Given the inherently ill-posed nature of hemodynamic deconvolution, due to the strong temporal
15 low-pass characteristics of the HRF, the key is to introduce additional constraints in the estimation problem that are typically expressed as regularizers. For instance, the so-called Wiener deconvolution is expressing a “minimal energy” constraint on the deconvolved signal, and has been used in the framework of psychophysiological interaction analysis to compute the interaction between a seed’s activity-inducing timecourse and an experimental modulation (Glover 1999; Gitelman et al.
20 2003; Gerchen et al. 2014; Di and Biswal 2018; Freitas et al. 2020). Complementarily, the interest in deconvolution has increased to explore time-varying activity in resting-state fMRI data (Prete et al. 2017; Keilholz et al. 2017; Lurie et al. 2020; Bolton et al. 2020). In that case, the aim is to gain better insights of the neural signals that drive functional connectivity at short time scales, as well as learning about the spatio-temporal structure of functional components that dynamically
25 construct resting-state networks and their interactions (Karahanoğlu and Ville 2017).

Deconvolution of the resting-state fMRI signal has illustrated the significance of transient, sparse spontaneous events (Petridou et al. 2012; Allan et al. 2015) that refine the hierarchical clusterization of functional networks (Karahanoğlu et al. 2013) and reveal their temporal overlap based on their signal innovations not only in the human brain (Karahanoğlu and Ville 2015), but also in the spinal cord (Kinany et al. 2020). Similar to task-related studies, deconvolution allows to investigate
30 modulatory interactions within and between resting-state functional networks (Di and Biswal 2013, 2015). In addition, decoding of the deconvolved spontaneous events allows to decipher the flow of spontaneous thoughts and actions across different cognitive and sensory domains while at rest (Karahanoğlu and Ville 2015; Gonzalez-Castillo et al. 2019; Tan et al. 2017). Beyond findings
35 on healthy subjects, deconvolution techniques have also proven its utility in clinical conditions to characterize functional alterations of patients with a progressive stage of multiple sclerosis at rest (Bommarito et al. 2020), to find functional signatures of prodromal psychotic symptoms and anxiety at rest on patients suffering from schizophrenia (Zöller et al. 2019), to detect the foci of interictal events in epilepsy patients without an EEG recording (Lopes et al. 2012; Karahanoglu
40 et al. 2013), or to study functional dissociations observed during non-rapid eye movement sleep that are associated with reduced consolidation of information and impaired consciousness (Tarun et al. 2020).

The algorithms for hemodynamic deconvolution can be classified based on the assumed hemodynamic model and the optimization problem used to estimate the neuronal-related signal. Most approaches assume a linear time-invariant model for the hemodynamic response that is inverted
45 by means of variational (regularized) least squares estimators (Glover 1999; Gitelman et al. 2003; Gaudes et al. 2010, 2012, 2013; Caballero-Gaudes et al. 2019; Hernandez-Garcia and Ulfarsson 2011; Karahanoğlu et al. 2013; Cherkaoui et al. 2019; Costantini et al. 2021; Hütel et al. 2021), logistic functions (Bush and Cisler 2013; Bush et al. 2015; Loula et al. 2018), probabilistic mixture models
50 (Pidnebesna et al. 2019), convolutional autoencoders (Hütel et al. 2018) or nonparametric homomorphic filtering (Sreenivasan et al. 2015). Alternatively, several methods have also been proposed to invert non-linear models of the neuronal and hemodynamic coupling (Riera et al. 2004; Friston et al. 2008; Havlicek et al. 2011; Aslan et al. 2016; Madi and Karameh 2017; Ruiz-Euler et al. 2018).

Among the variety of approaches, those based on regularized least squares estimators have been

55 employed more often due to their appropriate performance at small spatial scales (e.g., voxelwise).
 Relevant for this work, two different formulations can be established for the regularized least squares
 problem, either based on a synthesis- or analysis-based model (Elad et al. 2007; Ortelli and van de
 Geer 2019). The rationale of the synthesis-based model is that we know or suspect that the true
 signal (here, the neuronally-driven BOLD component of the fMRI signal) can be represented as a
 linear combination of predefined patterns or dictionary atoms (for instance, the hemodynamic re-
 sponse function). In contrast, the analysis-based approach considers that the true signal is analyzed
 by some relevant operator and the resulting signal is small (i.e., sparse).

60 This note revisits synthesis- and analysis-based deconvolution methods for fMRI data and com-
 prises four sections. In the first, we present the theory behind two state-of-the-art deconvolution
 approaches based on regularized least squares estimators that promote sparsity: Paradigm Free
 Mapping (PFM) (Gaudes et al. 2013) — available in AFNI as *3dPFM*¹ and *3dMEPFM*² for single-
 echo and multi-echo data, respectively — and Total Activation (TA) (Karahanoğlu et al. 2013) —
 available as part of the *iCAPs toolbox*³. We then assess their performance controlling for a fair
 comparison on simulated and experimental data. Finally, we discuss the benefits and shortcomings
 70 of each technique and conclude with our vision on potential extensions and developments.

2. Theory

2.1. Notations and definitions

Matrices of size N rows and M columns are denoted by boldface capital letters, e.g., $\mathbf{X} \in \mathbb{R}^{N \times M}$,
 whereas column vectors of length N are denoted as boldface lowercase letters, e.g., $\mathbf{x} \in \mathbb{R}^N$. Scalars
 75 are denoted by lowercase letters, e.g., k . Continuous functions are denoted by brackets, e.g., $h(t)$,
 while discrete functions are denoted by square brackets, e.g., $x[k]$. The euclidean norm of a matrix
 \mathbf{X} is denoted as $\|\mathbf{X}\|_2$, the ℓ_1 -norm is denoted by $\|\mathbf{X}\|_1$ and the Frobenius norm is denoted by
 $\|\mathbf{X}\|_F$. The discrete integration (\mathbf{L}) and difference (\mathbf{D}) operators are defined as:

$$\mathbf{L} = \begin{bmatrix} 1 & 0 & \dots \\ 1 & 1 & 0 & \dots \\ 1 & 1 & 1 & 0 & \dots \\ \vdots & \ddots & \ddots & \ddots & \ddots \end{bmatrix}, \quad \mathbf{D} = \begin{bmatrix} 1 & 0 & \dots \\ 1 & -1 & 0 & \dots \\ 0 & \ddots & \ddots & \ddots & \dots \\ \vdots & \ddots & 0 & 1 & -1 \end{bmatrix}.$$

2.2. Conventional general linear model analysis

Conventional general linear model (GLM) analysis puts forward a number of regressors incorpo-
 rating hypothetical knowledge about the paradigm or behavior. For instance, the timing of epochs
 for a certain condition can be modeled as an indicator function $p(t)$ (e.g., Dirac functions for event-
 related designs or box-car functions for block-designs) convolved with the hemodynamic response
 function (HRF) $h(t)$, and sampled at TR resolution (Friston et al. 1994, 1998; Boynton et al. 1996;
 Cohen 1997):

$$x(t) = p * h(t) \rightarrow x[k] = p * h(k \cdot \text{TR}).$$

¹https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dPFM.html

²https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dMEPFM.html

³<https://c4science.ch/source/iCAPs/>

The vector $\mathbf{x} = [x[k]]_{k=1,\dots,N} \in \mathbb{R}^N$ then constitutes the regressor modelling the hypothetical response, and several of them can be stacked as columns of the design matrix $\mathbf{X} = [\mathbf{x}_1 \dots \mathbf{x}_L] \in \mathbb{R}^{N \times L}$, leading to the well-known GLM formulation:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{e}, \quad (1)$$

where the empirical timecourse $\mathbf{y} \in \mathbb{R}^N$ is explained by a linear combination of the regressors in \mathbf{X} weighted by the parameters in $\boldsymbol{\beta} \in \mathbb{R}^L$ and corrupted by additive noise $\mathbf{e} \in \mathbb{R}^N$. Under independent and identically distributed Gaussian assumptions of the latter, the maximum likelihood estimate of the parameter weights reverts to the ordinary least-squares estimator; i.e., minimizing the residual sum of squares between the fitted model and measurements. The number of regressors L is typically much less than the number of measurements N , and thus the regression problem is over-determined and does not require additional constraints or assumptions.

In the deconvolution approach, no prior knowledge of the hypothetical response is taken into account, and the purpose is to estimate the deconvolved activity-inducing signal \mathbf{s} from the measurements \mathbf{y} , which can be formulated as the signal model

$$\mathbf{y} = \mathbf{H}\mathbf{s} + \mathbf{e}, \quad (2)$$

where $\mathbf{H} \in \mathbb{R}^{N \times N}$ is a Toeplitz matrix that represents the discrete convolution with the HRF, and $\mathbf{s} \in \mathbb{R}^N$ is a length- N vector with the unknown activity-inducing signal. Note that the temporal resolution of the activiy-inducing signal and the corresponding Toeplitz matrix is generally assumed to be equal to the TR of the acquisition, but it could also be higher if an upsampled estimate is desired. Despite the apparent similarity with the GLM equation, there are two important differences. First, the multiplication with the design matrix of the GLM is an expansion as a weighted linear combination of its columns, while the multiplication with the HRF matrix represents a convolution operator. Second, determining \mathbf{s} is an ill-posed problem given the nature of the HRF. As it can be seen intuitively, the convolution matrix \mathbf{H} is highly collinear (i.e., its columns are highly correlated) due to large overlap between shifted HRFs (see Figure 2C), thus introducing large variability in the estimates of \mathbf{s} . Consequently, additional assumptions under the form of regularization terms (or priors) in the estimate are needed to reduce their variance. In the least squares sense, the optimization problem to solve is given by

$$\hat{\mathbf{s}} = \arg \min_{\mathbf{s}} \frac{1}{2} \|\mathbf{y} - \mathbf{H}\mathbf{s}\|_2^2 + \Omega(\mathbf{s}). \quad (3)$$

The first term quantifies data fitness, which can be justified as the log-likelihood term derived from Gaussian noise assumptions, while the second term $\Omega(\mathbf{s})$ brings in regularization and can be interpreted as a prior on the activity-inducing signal. For example, the ℓ_2 -norm of \mathbf{s} (i.e., $\Omega(\mathbf{s}) = \lambda \|\mathbf{s}\|_2^2$) is imposed for ridge regression or Wiener deconvolution, which introduces a trade-off between the data fit term and “energy” of the estimates that is controlled by the regularization parameter λ .

2.3. Paradigm Free Mapping

In paradigm free mapping (PFM), the formulation of Eq. (3) was considered equivalently as fitting the measurements using the atoms of the HRF dictionary (i.e., columns of \mathbf{H}) with corresponding weights (entries of \mathbf{s}). This model corresponds to a synthesis formulation. In Gaudes et al. 2013 a sparsity-pursuing regularization term was introduced on \mathbf{s} , which in a strict way reverts to

choosing $\Omega(\mathbf{s}) = \lambda\|\mathbf{s}\|_0$ as the regularization term and solving the optimization problem (Bruckstein et al. 2009). However, finding the optimal solution to the problem demands an exhaustive search across all possible combinations of the columns of \mathbf{H} . Hence, a pragmatic solution is to solve the convex-relaxed optimization problem for the l_1 -norm, commonly known as Basis Pursuit Denoising (Chen et al. 2001) or equivalently as the least absolute shrinkage and selection operator (LASSO) (Tibshirani 1996):

$$\hat{\mathbf{s}} = \arg \min_{\mathbf{s}} \frac{1}{2} \|\mathbf{y} - \mathbf{H}\mathbf{s}\|_2^2 + \lambda\|\mathbf{s}\|_1, \quad (4)$$

which provides fast convergence to a global solution. Imposing sparsity on the activity-inducing signal implies that it is assumed to be well represented by a reduced subset of few non-zero coefficients at the fMRI timescale, which in turn trigger event-related BOLD responses. Hereinafter, we refer to this assumption as the *spike model*.

2.4. Total Activation

Alternatively, deconvolution can be formulated as if the signal to be recovered directly fits the measurements and at the same time satisfies some suitable regularization, which leads to

$$\hat{\mathbf{x}} = \arg \min_{\mathbf{x}} \frac{1}{2} \|\mathbf{y} - \mathbf{x}\|_2^2 + \Omega(\mathbf{x}). \quad (5)$$

Under this analysis formulation, total variation (TV), i.e., the ℓ_1 -norm of the derivative $\Omega(\mathbf{x}) = \lambda\|\mathbf{Dx}\|_1$, is a powerful regularizer since it favors recovery of piecewise-constant signals (Chambolle 2004). Going beyond, the approach of generalized TV introduces an additional differential operator $\mathbf{D}_\mathbf{H}$ in the regularizer that can be tailored as the inverse operator of a linear system (Karahanoglu et al. 2011), that is, $\Omega(\mathbf{x}) = \lambda\|\mathbf{DD}_\mathbf{H}\mathbf{x}\|_1$. In the context of hemodynamic deconvolution, Total Activation is proposed for which the discrete operator $\mathbf{D}_\mathbf{H}$ is derived from the inverse of the continuous-domain linearized Balloon-Windkessel model (Buxton et al. 1998; Friston et al. 2000). The interested reader is referred to (Khalidov et al. 2011; Karahanoglu et al. 2011; Karahanoglu et al. 2013) for a detailed description of this derivation.

Therefore, the solution of the Total Activation (TA) problem

$$\hat{\mathbf{x}} = \arg \min_{\mathbf{x}} \frac{1}{2} \|\mathbf{y} - \mathbf{x}\|_2^2 + \lambda\|\mathbf{DD}_\mathbf{H}\mathbf{x}\|_1 \quad (6)$$

will yield the activity-related signal \mathbf{x} for which the activity-inducing signal $\mathbf{s} = \mathbf{D}_\mathbf{H}\mathbf{x}$ and the so-called innovation signal $\mathbf{u} = \mathbf{Ds}$ will also be available, as they are required for the regularization. We refer to modelling the activity-inducing signal based on the innovation signal as the *block model*.

2.5. Unifying both perspectives

PFM and TA are based on the synthesis- and analysis-based formulation of the deconvolution problem, respectively. In the first case, the recovered deconvolved signal is synthesized to be matched to the measurements, while in the second case, the recovered signal is directly matched to the measurements but needs to satisfy its analysis in terms of deconvolution. This also corresponds to using the forward or backward model of the hemodynamic system, respectively. Hence, it should be possible to make both approaches equivalent (Elad et al. 2007)⁴.

⁴Without dwelling into technicalities, for total variation, this equivalence is correct up to the constant, which is in the null space of the derivative operator.

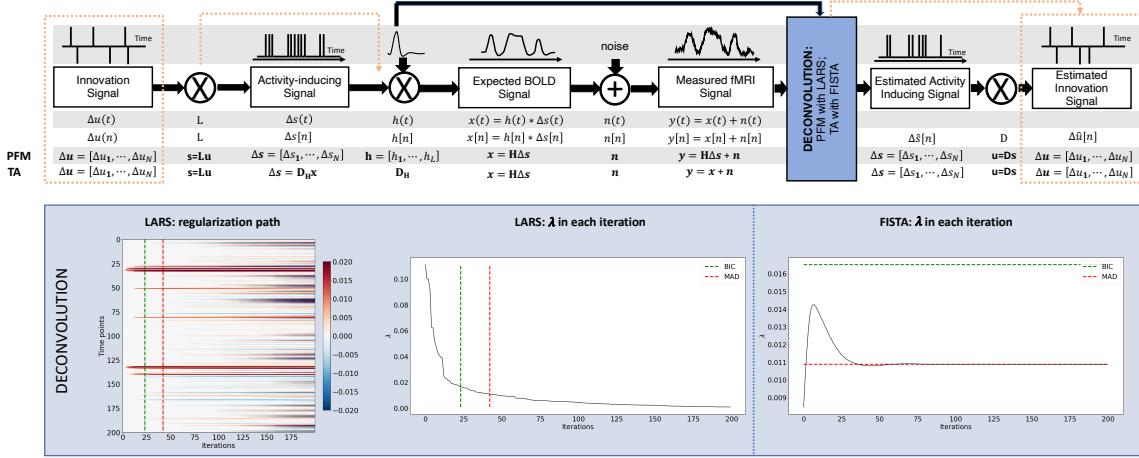


Figure 1: Flowchart detailing the different steps of the fMRI signal and the deconvolution methods described. The orange arrows indicate the flow to estimate the innovation signals. The blue box depicts the iterative *modus operandi* of the two algorithms used in this paper to solve the PFM and TA deconvolution problems. The plot on the left shows the regularization path obtained with LARS, where the x-axis illustrates the different iterations of the algorithm, the y-axis represents points in time, and the color describes the amplitude of the estimated signal. The middle plot depicts the decreasing values of λ for each iteration of LARS as the regularization path is computed. The green and red dashed lines in both plots illustrate the BIC and MAD solutions, respectively. Comparatively, the changes in λ when the FISTA method is made to converge to the MAD estimate of the noise are shown on the right. Likewise, the λ corresponding to the BIC and MAD solutions are shown with dashed lines.

To start with, TA can be made equivalent to PFM by removing the derivative operator \mathbf{D} of the regularizer in Eq. (6). It can then be readily verified that replacing in that case $\mathbf{x} = \mathbf{H}\mathbf{s}$ leads to identical equations and thus both assume a spike model, since \mathbf{H} and $\mathbf{D}_\mathbf{H}$ will cancel out each other (Karahanoglu et al. 2011)⁵.

Conversely, the PFM spike model from Eq. (4) can also be made equivalent to the TA block model in Eq. (6) by considering the modified forward model $\mathbf{y} = \mathbf{H}\mathbf{L}\mathbf{u} + \mathbf{e}$. Here, the activity-inducing signal \mathbf{s} is rewritten in terms of the innovation signal \mathbf{u} as $\mathbf{s} = \mathbf{L}\mathbf{u}$ where the matrix \mathbf{L} is the first-order integration operator (Cherkaoui et al. 2019; Uruñuela et al. 2020). This way, PFM can also estimate the innovation signal \mathbf{u} as follows:

$$\hat{\mathbf{u}} = \arg \min_{\mathbf{u}} \frac{1}{2} \|\mathbf{y} - \mathbf{H}\mathbf{L}\mathbf{u}\|_2^2 + \lambda \|\mathbf{u}\|_1, \quad (7)$$

and becomes equivalent to TA by replacing $\mathbf{u} = \mathbf{D}\mathbf{D}_\mathbf{H}\mathbf{x}$, and thus adopting the block model. This work evaluates the core of the two techniques, i.e., the regularized least-squares problem with temporal regularization without considering the spatial regularization term originally incorporated in TA.

⁵Again, this holds up to elements of the null space.

2.6. Algorithms and parameter selection

Despite their analytical equivalence, the PFM and TA methods proposed different strategies to solve the corresponding optimization problem and select an adequate regularization parameter λ . The PFM implementation available in AFNI employs the least angle regression (LARS) (Efron et al. 2004), whereas the TA implementation uses the fast iterative shrinkage-thresholding algorithm (FISTA) (Beck and Teboulle 2009). The blue box in Figure 1 provides a descriptive view of the iterative *modus operandi* of the two algorithms.

On the one hand, LARS is a homotopy approach that computes all the possible solutions to the optimization problem and their corresponding value of λ , i.e., the regularization path, and the solution according to the Bayesian Information Criterion (BIC) (Schwarz 1978) was recommended as the most appropriate in the case of PFM approaches (Gaudes et al. 2013; Caballero-Gaudes et al. 2019).

Alternatively, the regularization parameter λ can also be updated in every iteration of the FISTA so that the residuals of the data fit converge to a previously estimated noise level of the data $\hat{\sigma}$:

$$\lambda^{n+1} = \frac{N\hat{\sigma}}{\frac{1}{2}\|\mathbf{y} - \mathbf{x}^n\|_F^2} \lambda^n, \quad (8)$$

where x^n is the n^{th} iteration estimate, λ^n and λ^{n+1} are the n^{th} and $n + 1^{th}$ iteration values for the regularization parameter λ , and N is the number of points in the time-course. This pre-estimated noise level can be calculated as the median absolute deviation (MAD) of the fine-scale wavelet coefficients (Daubechies, order 3) of the fMRI timeseries. The MAD criterion has been adopted in TA (Karahanoglu et al. 2013). Of note, similar formulations based on the MAD estimate have also been applied in PFM formulations (Gaudes et al. 2012, 2011).

3. Methods

3.1. Simulated data

In order to compare the two methods while controlling for their correct performance, we created a simulation scenario that can be found in the GitHub repository shared in section 6. For the sake of illustration, we describe here the simulations corresponding to a timeseries with a duration of 400 seconds (TR = 2 s) where the activity-inducing signal includes 5 events, which are convolved with the canonical HRF. Different noise sources (physiological, thermal, and motion-related) were also added and we simulated three different scenarios with varying signal-to-noise ratios (SNR = [20 dB, 10 dB, 3 dB]) that represent high, medium and low contrast-to-noise ratios as shown in Figure 2A. Noise was created following the procedure in (Gaudes et al. 2013) as the sum of uncorrelated Gaussian noise and sinusoidal signals to simulate a realistic noise model with thermal noise, cardiac and respiratory physiological fluctuations, respectively. The physiological signals were generated as

$$\sum_{i=1}^2 \frac{1}{2^{i-1}} (\sin(2\pi f_{r,i}t + \phi_{r,i}) + \sin(2\pi f_{c,i}t + \phi_{c,i})), \quad (9)$$

with up to second-order harmonics per cardiac ($f_{c,i}$) and respiratory ($f_{r,i}$) component that were randomly generated following normal distributions with variance 0.04 and mean if_r and if_c , for $i = [1, 2]$. We set the fundamental frequencies to $f_r = 0.3$ Hz for the respiratory component (Birn et al. 2006) and $f_c = 1.1$ Hz for the cardiac component (Shmueli et al. 2007). The phases of each

harmonic ϕ were randomly selected from a uniform distribution between 0 and 2π radians. To simulate physiological noise that is proportional to the change in BOLD signal, a variable ratio between the physiological (σ_P) and the thermal (σ_0) noise was modeled as $\sigma_P/\sigma_0 = a(tSNR)^b + c$, where $a = 5.01 \times 10^{-6}$, $b = 2.81$, and $c = 0.397$, following the experimental measures available in Table 3 in (Triantafyllou et al. 2005).

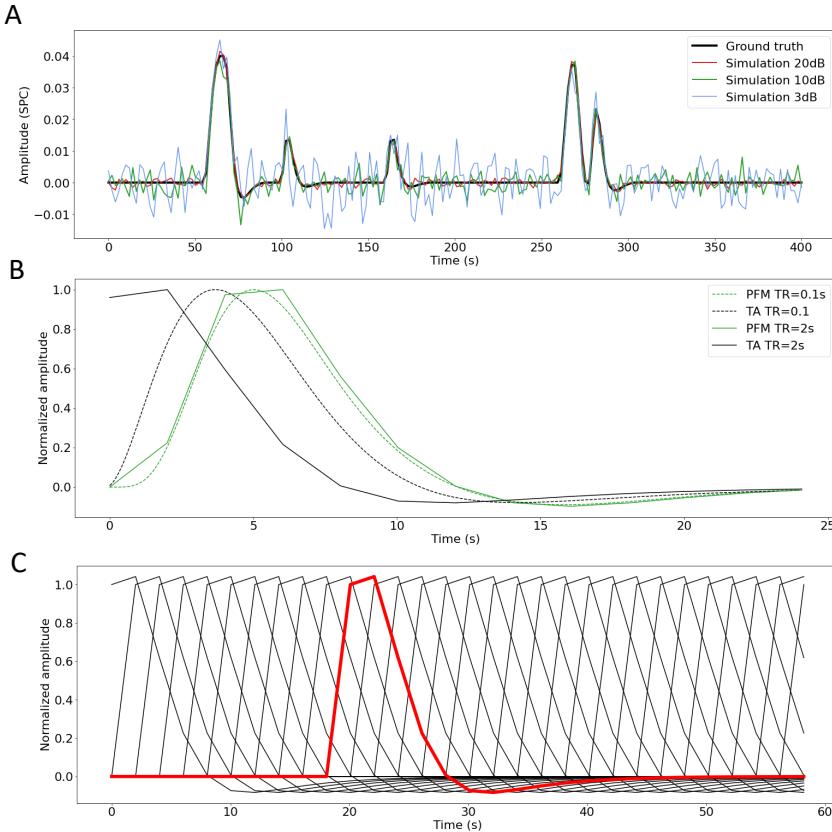


Figure 2: A) Simulated signal with different SNRs (20 dB, 10 dB and 3 dB) and ground truth given in signal percentage change (SPC). B) Canonical HRF models typically used by PFM (green) and TA (black) at TR = 0.1 s (dashed lines) and TR = 2 s (solid lines). Without loss of generality, the waveforms are scaled to unit amplitude for visualization. C) Representation of shifted HRFs at TR = 2 s that build the design matrix for PFM when the HRF model has been matched to that in TA. The red line corresponds to one of the columns of the HRF matrix.

155 3.2. Experimental data

To compare the performance of the two approaches as well as illustrate their operation, we employ two representative experimental datasets.

Motor task dataset: One healthy subject was scanned in a 3T MR scanner (Siemens) under a Basque Center on Cognition, Brain and Language Review Board-approved protocol. T2*-weighted multi-echo fMRI data was acquired with a simultaneous-multislice multi-echo gradient echo-planar

imaging sequence, kindly provided by the Center of Magnetic Resonance Research (University of Minnesota, USA) (Feinberg et al. 2010; Moeller et al. 2010; Setsopop et al. 2011), with the following parameters: 340 scans, 52 slices, Partial-Fourier = 6/8, voxel size = $2.4 \times 2.4 \times 3$ mm³, TR = 1.5 s, TEs = 10.6/28.69/46.78/64.87/82.96 ms, flip angle = 70°, multiband factor = 4, GRAPPA = 2.

During the fMRI acquisition, the subject performed a motor task consisting of five different movements (left-hand finger tapping, right-hand finger tapping, moving the left toes, moving the right toes and moving the tongue) that were visually cued through a mirror located on the head coil. These conditions were randomly intermixed every 16 seconds, and were only repeated once the entire set of stimuli were presented. Data preprocessing consisted of first, discarding the first 10 volumes of the functional data to achieve a steady state of magnetization. Then, image realignment to the skull-stripped single-band reference image (SBRef) was computed on the first echo, and the estimated rigid-body spatial transformation was applied to all other echoes (Jenkinson et al. 2012; Jenkinson and Smith 2001). A brain mask obtained from the SBRef volume was applied to all the echoes and the different echo timeseries were optimally combined (OC) voxelwise by weighting each timeseries contribution by its T2* value (Posse et al. 1999). AFNI (Cox 1996) was employed for a detrending of up to 4th-order Legendre polynomials, within-brain spatial smoothing (3 mm FWHM) and voxelwise signal normalization to percentage change. Finally, distortion field correction was performed on the OC volume with Topup (Andersson et al. 2003), using the pair of spin-echo EPI images with reversed phase encoding acquired before the ME-EPI acquisition (Glasser et al. 2016).

Resting-state datasets: One healthy subject was scanned in a 3T MR scanner (Siemens) under a Basque Center on Cognition, Brain and Language Review Board-approved protocol. Two runs of T2*-weighted fMRI data were acquired during resting-state, each with 10 min duration, with 1) a standard gradient-echo echo-planar imaging sequence (monoband) (TR = 2000 ms, TE = 29 ms, flip-angle = 78°, matrix size = 64 × 64, voxel size = 3 × 3 × 3 mm³, 33 axial slices with interleaved acquisition, slice gap = 0.6 mm) and 2) a simultaneous-multislice gradient-echo echo-planar imaging sequence (multiband factor = 3, TR = 800 ms, TE = 29 ms, flip-angle = 60°, matrix size = 64 × 64, voxel size = 3 × 3 × 3 mm³, 42 axial slices with interleaved acquisition, no slice gap). Single-band reference images were also collected in both resting-state acquisitions for head motion realignment. Field maps were also obtained to correct for field distortions.

During both acquisitions, participants were instructed to keep their eyes open, fixating a white cross that they saw through a mirror located on the head coil, and not to think about anything specific. The data was pre-processed using AFNI (Cox 1996). First, volumes corresponding to the initial 10 seconds were removed to allow for a steady-state magnetization. Then, the voxel time-series were despiked to reduce large-amplitude deviations and slice-time corrected. Inhomogeneities caused by magnetic susceptibility were corrected with FUGUE (FSL) using the field map images (Jenkinson et al. 2012). Next, functional images were realigned to a base volume (monoband: volume with the lowest head motion; multiband: single-band reference image). Finally, a simultaneous nuisance regression step was performed comprising up to 6th-order Legendre polynomials, low-pass filtering with a cutoff frequency of 0.25 Hz (only on multiband data to match the frequency content of the monoband), 6 realignment parameters plus temporal derivatives, 5 principal components of white matter (WM), 5 principal components of lateral ventricle voxels (anatomical CompCor) (Behzadi et al. 2007) and 5 principal components of the brain's edge voxels ,(Patriat et al. 2015). WM, CSF and brain's edge-voxel masks were obtained from Freesurfer tissue and brain segmentations. In addition, scans with potential artifacts were identified and censored when the euclidean norm of the temporal derivative of the realignment parameters (ENORM) was larger than 0.4, and the

proportion of voxels adjusted in the despiking step exceeded 10%.

3.3. Selection of the hemodynamic response function

By default, PFM and TA employ different shapes of the discrete-time hemodynamic response functions to estimate neuronal-related signals: the canonical HRF in the case of PFM, and an HRF resulting from the linear differential operator \mathbf{D}_H in the case of TA. Their temporal patterns are shown in Figure 2B. Consequently, to ensure a fair comparison between the two methods, we build the synthesis operator \mathbf{H} with shifted versions of the HRF given by the analysis operator (see Figure 2C), taking advantage of its versatile structure.

3.4. Selection of the regularization parameter

We use the simulated data to compare the performance of the two deconvolution algorithms with both BIC and MAD criteria to choose the regularization parameter λ (see section 2.6). We also evaluate if the algorithms behave differently in terms of the estimation of the activity-inducing signal \hat{s} using the spike model described in (4) and the block model based on the innovation signal $\hat{\mathbf{u}}$ in (7).

For selection based on the BIC, LARS was initially performed with the PFM deconvolution model to obtain the solution for every possible λ in the regularization path. Then, the values of λ corresponding to the BIC optimum were adopted to solve the TA deconvolution model by means of FISTA.

For a selection based on the MAD estimate of the noise, we apply the temporal regularization in its original form for TA, whereas for PFM the selected λ corresponds to the solution whose residuals have the closest standard deviation to the estimated noise level of the data $\hat{\sigma}$.

3.5. Analyses in experimental fMRI data

Difference between approaches: To assess the extent of the discrepancies between both approaches when applied on experimental fMRI data, we calculate the sum of squares of the differences (SSD) between the activity-inducing signals estimated with PFM and TA on the three experimental datasets as

$$SSD = \frac{\sum_k (\hat{s}_{\text{PFM}}[k] - \hat{s}_{\text{TA}}[k])^2}{N}, \quad (10)$$

where N is the number of timepoints of the acquisition. The SSD of the innovation signals $\hat{\mathbf{u}}$ was computed equally.

Task fMRI data: In the analysis of the motor task data, we evaluate the performance of PFM and TA in comparison with a conventional General Linear Model analysis (*3dDeconvolve* in AFNI) that takes advantage of the information about the duration and onsets of the motor trials. Given the block design of the motor task, we only make this comparison with the block model.

Resting-state fMRI data: We also illustrate the usefulness of deconvolution approaches in the analysis of resting-state data where information about the timings of neuronal-related BOLD activity cannot be predicted. Apart from being able to explore individual maps of deconvolved activity (i.e., innovation signals, activity-inducing signals or hemodynamic signals) at the temporal resolution of the acquisition (or deconvolution), here we calculate the co-activation patterns (CAPs) and innovation-driven co-activation patterns (iCAPs) from the obtained activity-inducing and innovation signals. To achieve this, we calculate the average time-series in a seed of 9 voxels located in the precuneus, supramarginal gyrus and occipital gyri independently, and solve the deconvolution

problem to find the activity-inducing and innovation signals in the seeds. We then apply a 95th percentile threshold and average the maps of the time-frames that survive the threshold. Finally, we apply the same procedure to the original— i.e., non-deconvolved— signal in the seed and compare the results with the widely-used seed correlation approach.

4. Results

4.1. Performance based on the regularization parameter

Figure 3A shows the regularization paths of PFM and TA side by side obtained for the spike model in Eq. (4) for SNR=3 dB. The solutions for all three SNR conditions are shown in Figures S1 and S2. Starting from the maximum λ corresponding to a null estimate and for decreasing values of λ , LARS computes a new estimate at the value of λ that reduces the sparsity promoted by the l_1 -norm and causes a change in the active set of non-zero coefficients of the estimate (i.e., a zero coefficient becomes non-zero or vice versa) as shown in the x-axis of the heatmaps. Vertical dashed lines depict the selection of the regularization parameter based on the BIC, and thus, the colored coefficients indicated by these depict the estimated activity-inducing signal \hat{s} . Figure 3B illustrates the resulting estimates of the activity-inducing and activity-related hemodynamic signals when basing the selection of λ on the BIC for SNR=3 dB. Given that the regularization paths of both approaches are identical, it can be clearly observed that the BIC-based estimates are identical too for the corresponding λ . Thus, Figures 3A, 3B, S1 and S2 demonstrate that, regardless of the simulated SNR condition, the spike model of both deconvolution algorithms produces identical regularization paths when the same HRF and regularization parameters are applied, and hence, identical estimates of the activity-inducing signal \hat{s} and neuronal-related hemodynamic signal \hat{x} . Likewise, Figure 3C demonstrates that the regularization paths for the block model defined in Eqs. (6) and (7) also yield virtually identical estimates of the innovation signals for both PFM and TA methods. Again, the BIC-based selection of λ is identical for both PFM and TA. As illustrated in Figure 3D, the estimates of the innovation signal u also show no distinguishable differences between the algorithms.

As for selecting λ with the MAD criterion defined in Eq. (8), Figure 3E depicts the estimated activity-inducing and activity-related signals for the simulated low-SNR setting using the spike model, while Figure 3F shows the estimated signals corresponding to the block model. Both plots in Figure 3E and F depict nearly identical results between PFM and TA with both models. Given that the regularization paths of both techniques are identical, minor differences are owing to the slight dissimilarities in the selection of λ due to the discrete nature of the values returned by LARS.

4.2. Performance on experimental data

Figure 4 depicts the sum of squared difference (SSD) between PFM and TA estimates of the spike (Figure 4A and C) and block (Figure 4B and D) models for the three experimental fMRI datasets. The SSD values are virtually negligible (i.e., depicted in yellow) in most of the within-brain voxels and clearly lower than the amplitude of the estimates of the activity-inducing and innovation signals. Based on the maximum value of the range shown in each image, we observe that the similarity between both approaches is more evident for the spike model (with both selection criteria) and the block model with the BIC selection. However, a selection of the regularization parameter λ based on the MAD estimate of the noise using the block model produces higher SSD values, with the largest differences occurring in gray matter voxels. These areas also correspond to

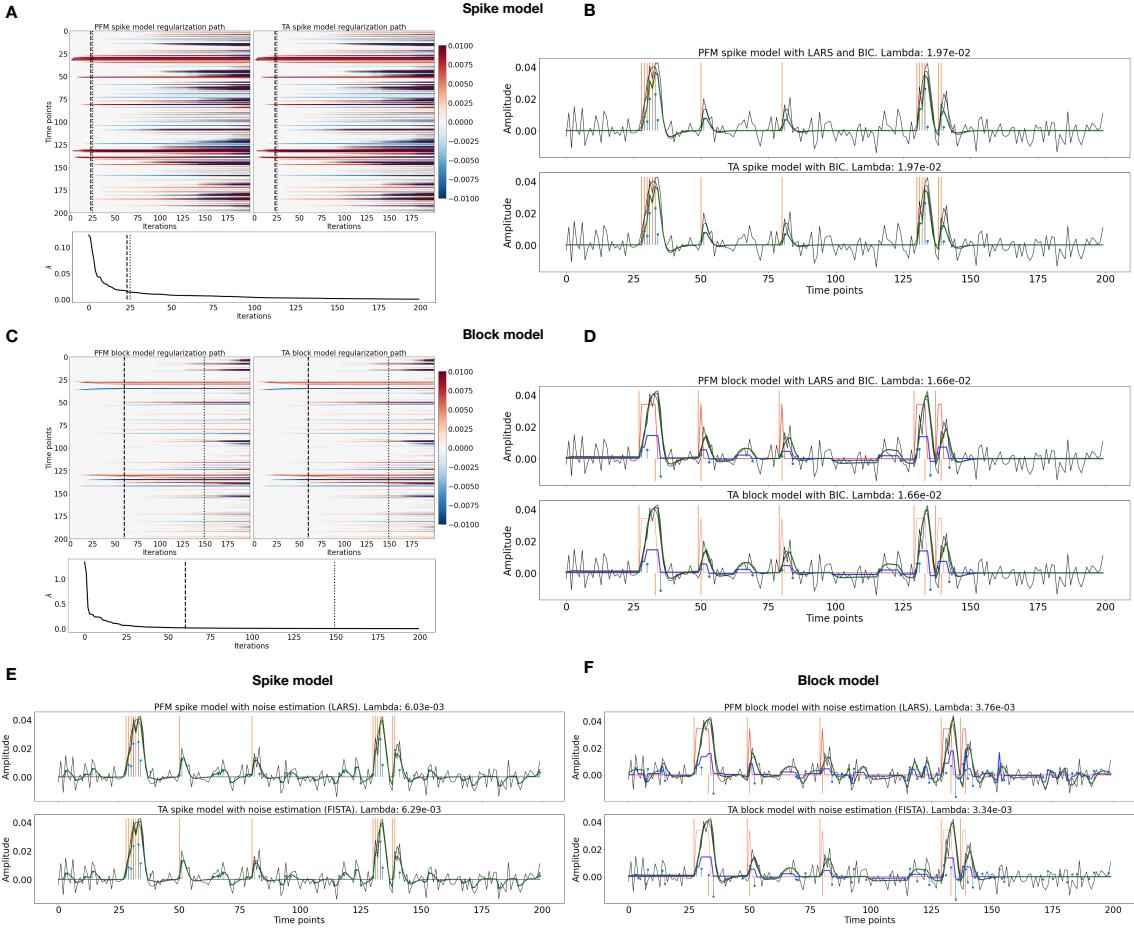


Figure 3: (A) Heatmap of the regularization paths of the activity-inducing signals (spike model) estimated with PFM and TA as a function of λ for the simulated data with SNR = 3 dB (x-axis: increasing number of iterations or λ as given by LARS; y-axis: time; color: amplitude). Vertical lines denote iterations corresponding to the BIC (dashed line) and MAD (dotted line) selection of λ . (B) Estimated activity-inducing (blue) and activity-related (green) signals with a selection of λ based on the BIC. Orange and red lines depict the ground truth. (C) Heatmap of the regularization paths of the innovation signals (block model) estimated with PFM and TA as a function of λ for the simulated data with SNR = 3 dB. (D) Estimated innovation (blue), activity-inducing (darker blue), and activity-related (green) signals with a selection of λ based on the BIC. (E) Activity-inducing and activity-related (fit, χ) signals estimated with PFM (top) and TA (bottom) when λ is selected based on the MAD method with the spike model, and (F) with the block model for the simulated data with SNR = 3 dB.

285 low values of λ (see Figure S3) and MAD estimates of the noise (see Figure S4), while the highest values are visible in regions with signal dropouts, ventricles, and white matter.

Figure 5 depicts the results of the analysis of the Motor dataset with the PFM and TA algorithms using the BIC selection of λ (see Figure S5 for results with MAD selection), as well as a conventional GLM approach. The Activation Time Series (top left), calculated as the sum of squares of all voxel

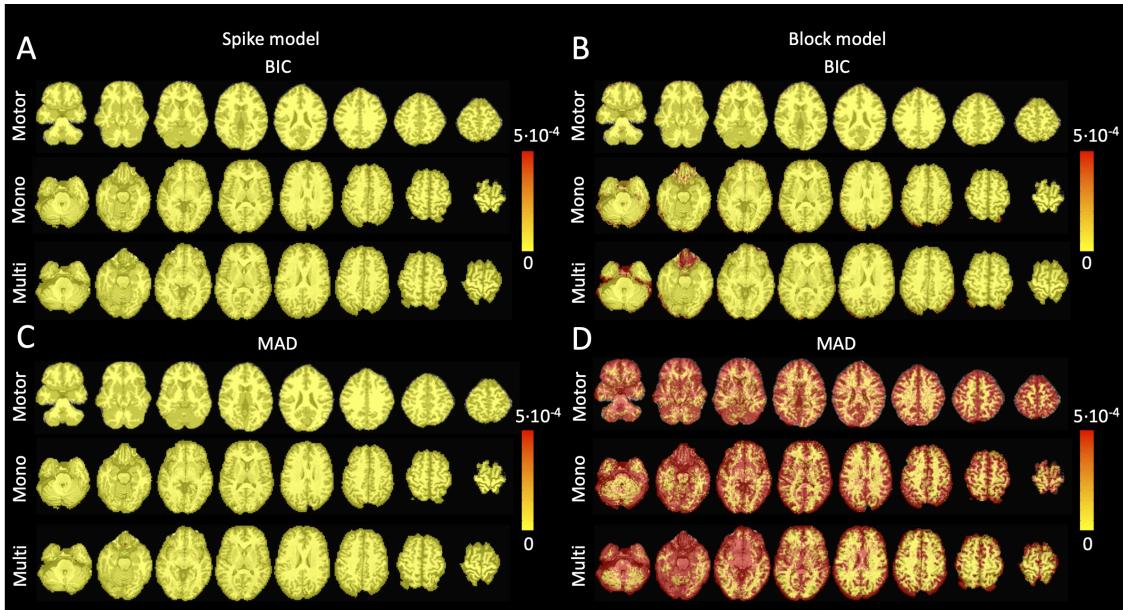


Figure 4: Sum of squared differences (SSD) between the estimates obtained with PFM and TA for (A) spike model (activity-inducing signal) and BIC selection of λ , (B) block model (innovation signal) and BIC selection, (C) spike model (activity-inducing signal) and MAD selection, (D) block model (innovation signal) and MAD selection. SSD maps are shown for the three experimental fMRI datasets: the motor task (Motor), the monoband resting-state (Mono), and the multiband resting-state (Multi) datasets.

amplitudes (positive vs. negative) for a given moment in time, obtained with PFM and TA show nearly identical patterns. These ATS help to summarize the four dimensional information available in the results across the spatial domain and identify instances of significant BOLD activity. Note that the differences observed with the block model and a selection of λ based on the MAD estimate shown in Figure 4 are reflected on the ATS shown in Figure S5. Returning to Figure 5, the second to sixth rows show the voxel timeseries and the corresponding activity-related, activity-inducing and innovation signals obtained with PFM using the BIC criterion of representative voxels in the regions activated in each of the motor tasks. The TA-estimated time-series are not shown because they were equivalent. The maps shown on the right correspond to statistical parametric maps obtained with the GLM for each motor condition ($p < 0.001$) as well as the maps of the PFM and TA estimates at the onsets of individual motor events (indicated with arrows in the timecourses). The estimated activity-related, activity-inducing and innovation signals clearly reveal the activity patterns of each condition in the task, as they exhibit a BOLD response locked to the onset and duration of the conditions. Overall, activity maps of the innovation signal obtained with PFM and TA highly resemble those obtained with a GLM for individual events.

As an illustration of the insights that deconvolution methods can provide in the analysis of resting-state data, Figure 6 depicts the CAPs and iCAPs obtained from thresholding and averaging the activity-inducing and innovation signals, respectively, estimated from the resting-state multiband data using PFM with a selection of λ based on the BIC. The activity-inducing CAPs obtained via deconvolution show spatial patterns of the default mode network (DMN), dorsal attention net-

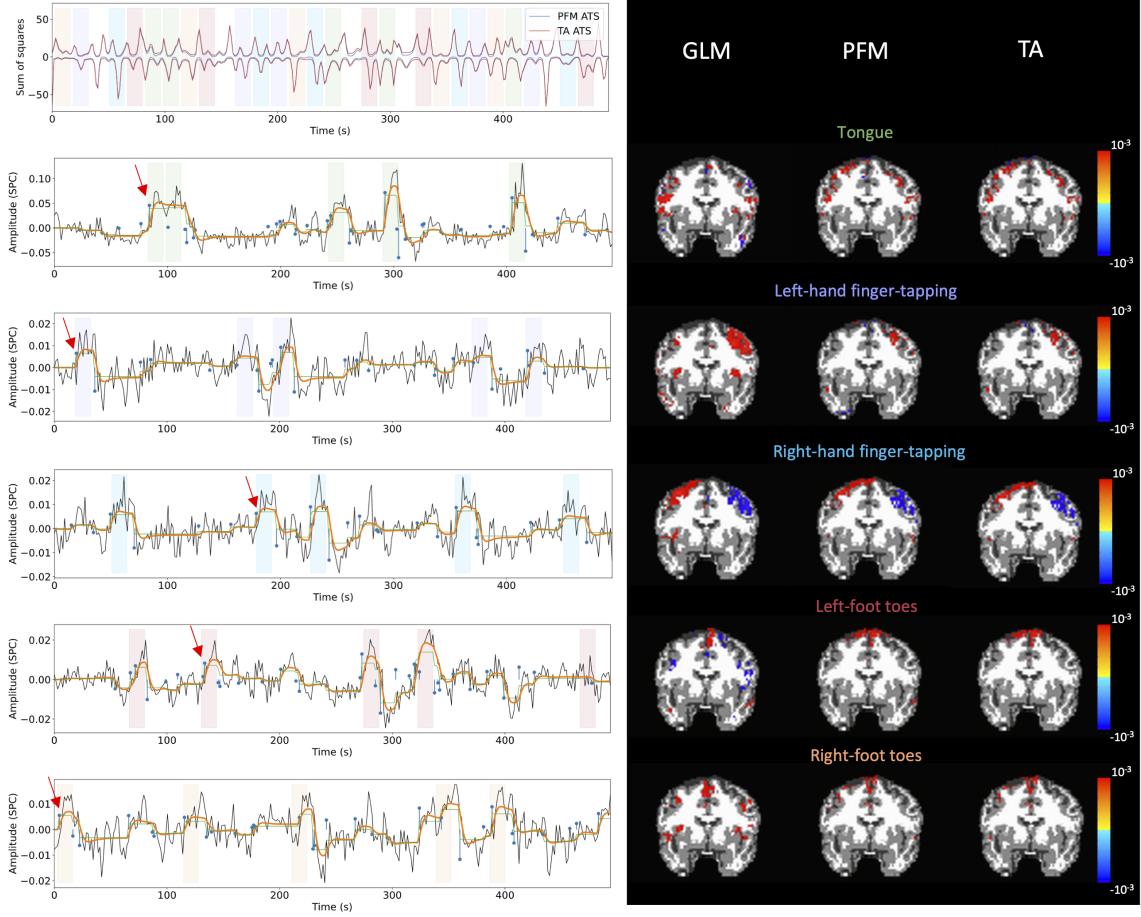


Figure 5: Activity maps of the motor task using a selection of λ based on the BIC estimate. Row 1: Activation time-series (ATS) of the innovation signals estimated by PFM (in blue) or TA (in red) calculated as the sum of squares of all voxels at every timepoint. Positive-valued and negative-valued contributions were separated into two distinct time-courses. Color-bands indicate the onset and duration of each condition in the task (green: tongue motion, purple: left-hand finger-tapping, blue: right-hand finger-tapping, red: left-foot toes motion, orange: right-foot toes motion). Rows 2-6: time-series of a representative voxel for each task with the PFM-estimated innovation (blue), PFM-estimated activity-inducing (green), and activity-related (i.e., fitted, orange) signals, with their corresponding GLM, PFM, and TA maps on the right. Amplitudes are given in signal percentage change (SPC). The maps shown on the right are sampled at the time-points labeled with the red arrows and display the innovation signals at these moments across the whole brain.

work (DAN) and visual network (VIS) that highly resemble the maps obtained with conventional seed correlation analysis using Pearson's correlation, and the CAPs based on the amplitude of the signal (i.e., with no deconvolution). With deconvolution, the CAPs seem to depict less spurious voxels (mainly negative) and more accurate spatial delineation (i.e., less smoothness) than those obtained from the original data, while maintaining the structure of the networks. The BIC-informed selection of λ yields spatial patterns of CAPs and iCAPs that are more sparse than those obtained

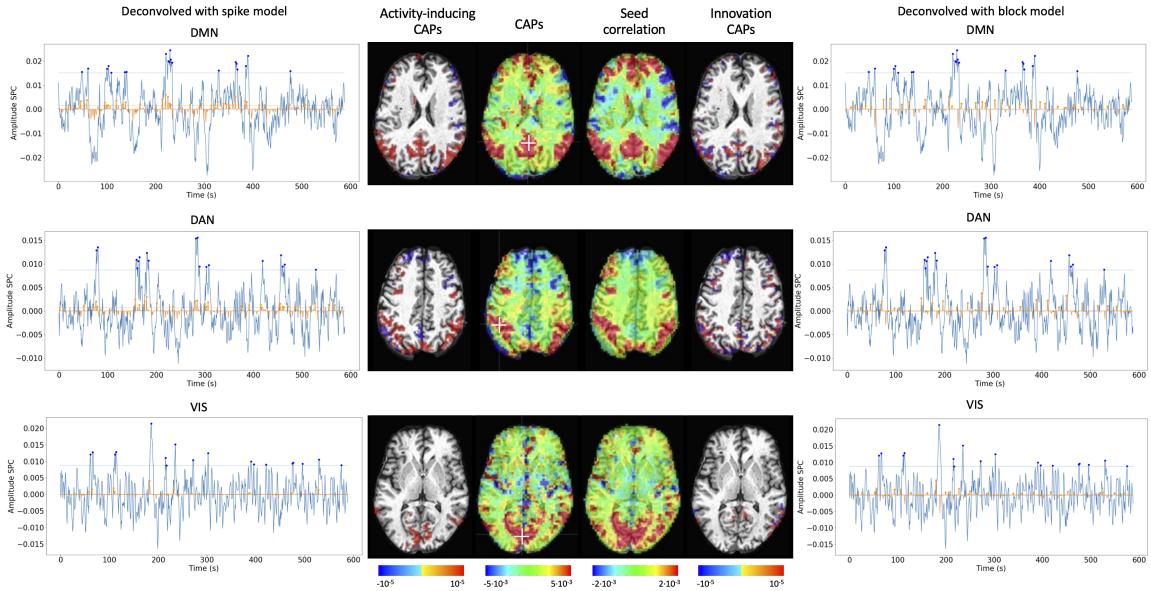


Figure 6: Activity-inducing co-activation patterns (activity-inducing CAPs, left) and innovation-driven co-activation patterns (innovation CAPs, right) obtained from PFM-estimated activity-inducing and innovation signals, respectively, using a BIC-based selection of λ . Time-points selected with a 95th percentile threshold (horizontal lines) are shown over the average time-series (blue) in the seed region (white cross) and the deconvolved signals, i.e., activity inducing (left) and innovation (right) signals (orange). CAPs and seed correlation maps are illustrated in the center.

with a selection of λ based on the MAD estimate (see Figure S6). Furthermore, the spatial patterns of the iCAPs based on the innovation signals using the block model yield complementary information to those obtained with the activity-inducing signal since iCAPs allow to reveal regions with synchronous innovations, i.e., with the same upregulating and downregulating events. For instance, it is interesting to observe that the structure of the visual network nearly disappears in its corresponding iCAP, suggesting the existence of different temporal neuronal patterns across voxels in the primary and secondary visual cortices.

5. Discussion

Hemodynamic deconvolution can be formulated using a synthesis- and analysis-based approach, which was proposed by PFM and TA, respectively. This work demonstrates that the theoretical equivalence of PFM and TA is confirmed in practice given virtually identical results when the same HRF model and equivalent regularization parameters are employed. Hence, we argue that previously observed differences in performance can be explained by specific settings, such as the HRF model and selection of the regularization parameter, convergence thresholds, as well as the addition of a spatial regularization term in the spatiotemporal TA formulation Karahanoğlu et al. 2013. However, given the equivalence of the temporal deconvolution, incorporating extra spatial or temporal regularization terms in the optimization problem should not modify this equivalence providing convex operators are employed. For a convex optimization problem, with a unique global

solution, iterative shrinkage thresholding procedures alternating between the different regularization terms guarantee convergence; e.g., the generalized forward-backward splitting (Raguet et al. 2013) algorithm originally employed for TA. Our findings are in line with the equivalence of analysis and synthesis methods in under-determined cases ($N \leq V$) demonstrated in (Elad et al. 2007) and (Ortelli and van de Geer 2019). Still, we have shown that a slight difference in the selection of the regularization parameter can lead to small differences in the estimated signals when employing the block model with the MAD selection of λ . However, since their regularization paths are equivalent, the algorithms can easily be forced to converge to the same selection of λ , thus resulting in identical estimated signals.

Nevertheless, the different formulations of analysis and synthesis deconvolution models bring along different kinds of flexibility. One notable advantage of PFM is that it can readily incorporate any HRF as part of the synthesis operator (Elad et al. 2007), only requiring the sampled HRF at the desired temporal resolution, which is typically equal to the TR of the acquisition. Conversely, TA relies upon the specification of the discrete differential operator that inverts the HRF, which needs to be derived either by the inverse solution of the sampled HRF impulse response, or by discretizing a continuous-domain differential operator motivated by a biophysical model. This more versatile structure of PFM allows for instance an elegant extension of the algorithm to multi-echo fMRI data (Caballero-Gaudes et al. 2019) where multiple measurements relate to a common underlying signal. Such one-to-many (i.e., from activity-inducing to several activity-related signals) formulation cannot be elegantly enforced using TA. One flexibility of TA though is the specification of block models through the derivative instead of the integrator of PFM, which impacts the stability and rate of the convergence of the algorithms. Extensions using combinations of spike and block regularizers are also easier to conceive using TA. Moreover, analysis formulations can be more suitable for online applications that are still to be explored in fMRI data but are widely employed for calcium imaging deconvolution (Friedrich et al. 2017; Jewell et al. 2019).

Deconvolution techniques can be used before more downstream analysis of brain activity in terms of functional network organization as they estimate interactions between voxels or brain regions that occur at the activity-inducing level, and are thus less affected by the slowness of the hemodynamic response compared to when the BOLD signals are analyzed directly. In addition, deconvolution approaches hold a close parallelism to recent methodologies aiming to understand the dynamics of neuronal activations and interactions at short temporal resolution and that focus on extreme events of the fMRI signal (Lindquist et al. 2007). As an illustration, Figure 6 shows that the innovation- or activity-inducing CAPs computed from deconvolved events in a single resting-state fMRI dataset closely resemble the conventional CAPs computed directly from extreme events of the fMRI signal (Liu and Duyn 2013; Liu et al. 2013, 2018; Cifre et al. 2020a,b; Zhang et al. 2020; Tagliazucchi et al. 2011, 2012, 2016; Rolls et al. 2021). Similarly, we hypothesize that these extreme events will also show a close resemblance to intrinsic ignition events (Deco and Kringelbach 2017; Deco et al. 2017). As shown in the maps, deconvolution approaches can offer a more straightforward interpretability of the activation events and resulting functional connectivity patterns. Here, CAPs were computed as the average of spatial maps corresponding to the events of a single dataset. Beyond simple averaging, clustering algorithms (e.g., K-means and consensus clustering) can be employed to discern multiple CAPs or iCAPs at the whole-brain level for a large number of subjects. Previous findings based on iCAPs have for instance revealed organizational principles of brain function during rest (Karahanoğlu and Ville 2015) and sleep (Tarun et al. 2021) in healthy controls, next to alterations in 22q11ds (Zoeller et al. 2019) and multiple sclerosis (Bommarito et al. in press). Next to CAPs-inspired approaches, dynamic functional connectivity has recently been investigated

380 with the use of co-fluctuations and edge-centric techniques (Faskowitz et al. 2020; Esfahlani et al. 2020; Jo et al. 2021; Sporns et al. 2021; van Oort et al. 2018). The activation time series shown in Figure 5 aims to provide equivalent information to the root of sum of squares timecourses used in edge-centric approaches, where timecourses with peaks delineate instances of significant brain activity. Future work could address which type of information is redundant or distinct across these
385 frameworks. In summary, these examples illustrate that deconvolution techniques can be employed prior to other computational approaches and could serve as an effective way of denoising the fMRI data. We foresee an increase in the number of studies that take advantage of the potential benefits of using deconvolution methods prior to functional connectivity analyses.

In sum, hemodynamic deconvolution approaches using sparsity-driven regularization are valuable tools to complete the fMRI processing pipeline. Current approaches already provide access to alternative representations of the BOLD signals in terms of innovation and activity-inducing signals. One relevant focus for future developments is to account for HRF variability, such as by using structured regularization terms along with multiple basis functions (Gaudes et al. 2012) or procedures that estimate the HRF shape in an adaptive fashion in both analysis (Farouj et al. 395 2019) and synthesis formulations (Cherkaoui et al. 2020a). Another avenue of research consists in multivariate deconvolution approaches that operate at the whole-brain level, instead of voxelwise, for instance using low rank decompositions (Cherkaoui et al. 2020a; Uruñuela et al. 2021) or group (a.k.a. mixed norm) regularization terms (Uruñuela-Tremiño et al. 2019). Methods for a more robust selection of the regularization parameter could also be explored, for instance, based on stability selection (Meinshausen and Bühlmann 2010; Uruñuela et al. 2020). Furthermore, the use of 400 non-convex $\ell_{p,q}$ -norm regularization terms (e.g., $p < 1$) could avoid the extra debiasing step that is necessary to overcome the shrinkage towards zero of the estimates and obtain a more accurate and less biased fit of the fMRI signal (Gaudes et al. 2013; Caballero-Gaudes et al. 2019). Alternatively, recent developments on physics-informed deep learning for inverse problems (Akçakaya et al. 2021; 405 Monga et al. 2021; Ongie et al. 2020; Cherkaoui et al. 2020b) could be transposed by considering the biophysical model of the hemodynamic system and potentially provide algorithms with reduced computational time and more flexibility.

6. Code and data availability

The code and materials used in this work can be found in the following GitHub repository:
410 https://github.com/eurunuela/pfm_vs_ta. We encourage the reader to explore the parameters (e.g., SNR, varying HRF options and mismatch between algorithms, TR, number of events, onsets, and durations) in the provided Jupyter notebooks. Likewise, the data used to produce the figures can be found in <https://osf.io/f3ryg/>.

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8. CRediT

Eneko Uruñuela: Conceptualisation, Methodology, Software, Formal Analysis, Investigation, Data Curation, Writing (OD), Writing (RE), Visualisation, Funding acquisition. Thomas A.W. Bolton: Conceptualisation, Methodology, Writing (RE). Dimitri Van de Ville: Conceptualisation, Methodology, Writing (RE). César Caballero-Gaudes: Conceptualisation, Methodology, Software, Formal Analysis, Investigation, Data Curation, Writing (OD), Writing (RE), Visualisation, Funding acquisition.

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Supplementary Material for Hemodynamic Deconvolution Demystified: Sparsity-Driven Regularization at Work

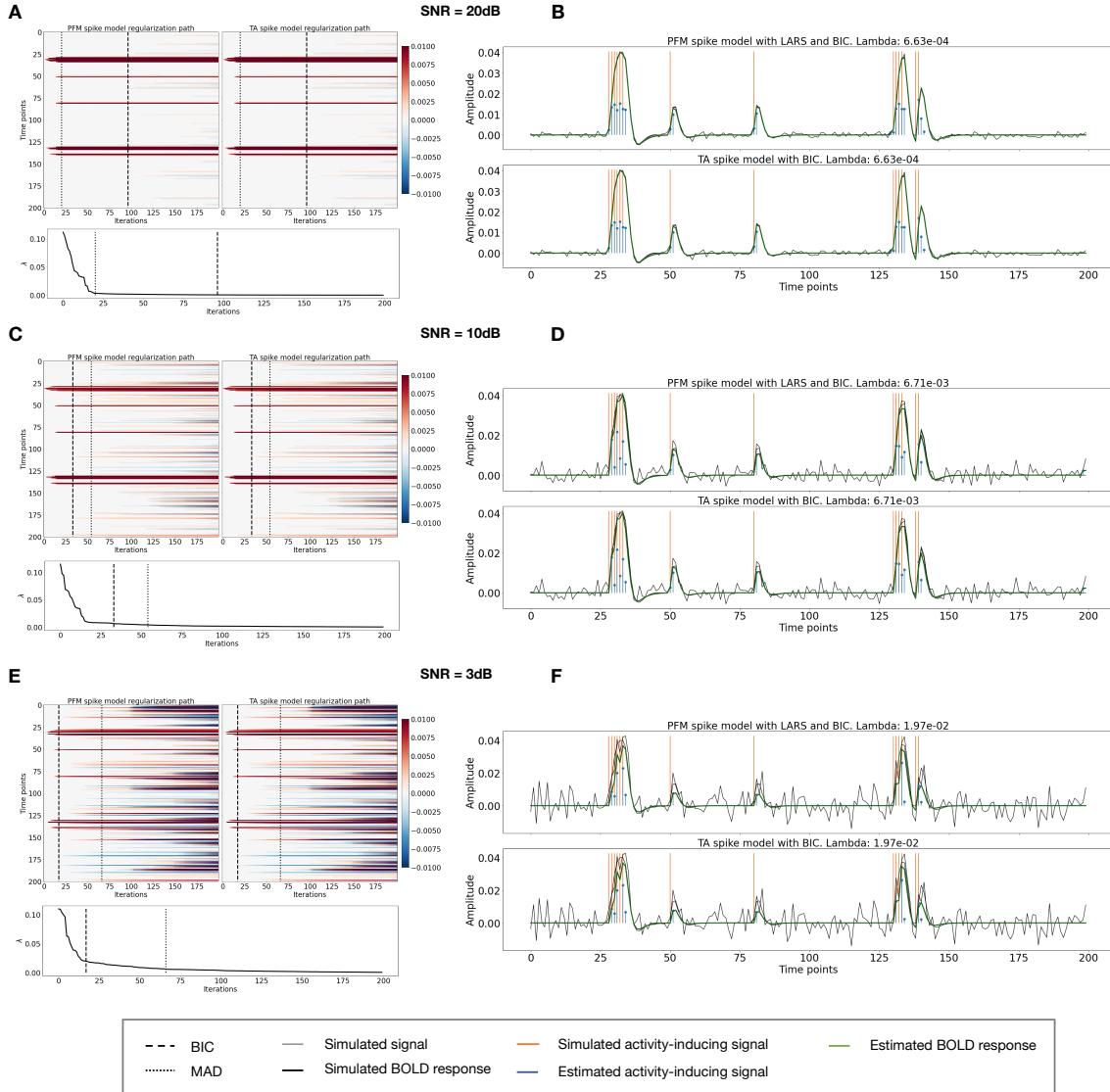


Figure S1: Spike model simulations. (Left) Heatmap of the regularization paths of the activity-inducing signal estimated with PFM and TA as a function of λ (increasing number of iterations in x-axis), whereas each row in the y-axis shows one time-point. Vertical lines denote iterations corresponding to the Akaike and Bayesian Information Criteria (AIC and BIC) optima. (Right) Estimated activity-inducing (blue) and activity-related (green) signals when set based on BIC. All estimates of are identical, regardless of SNR.

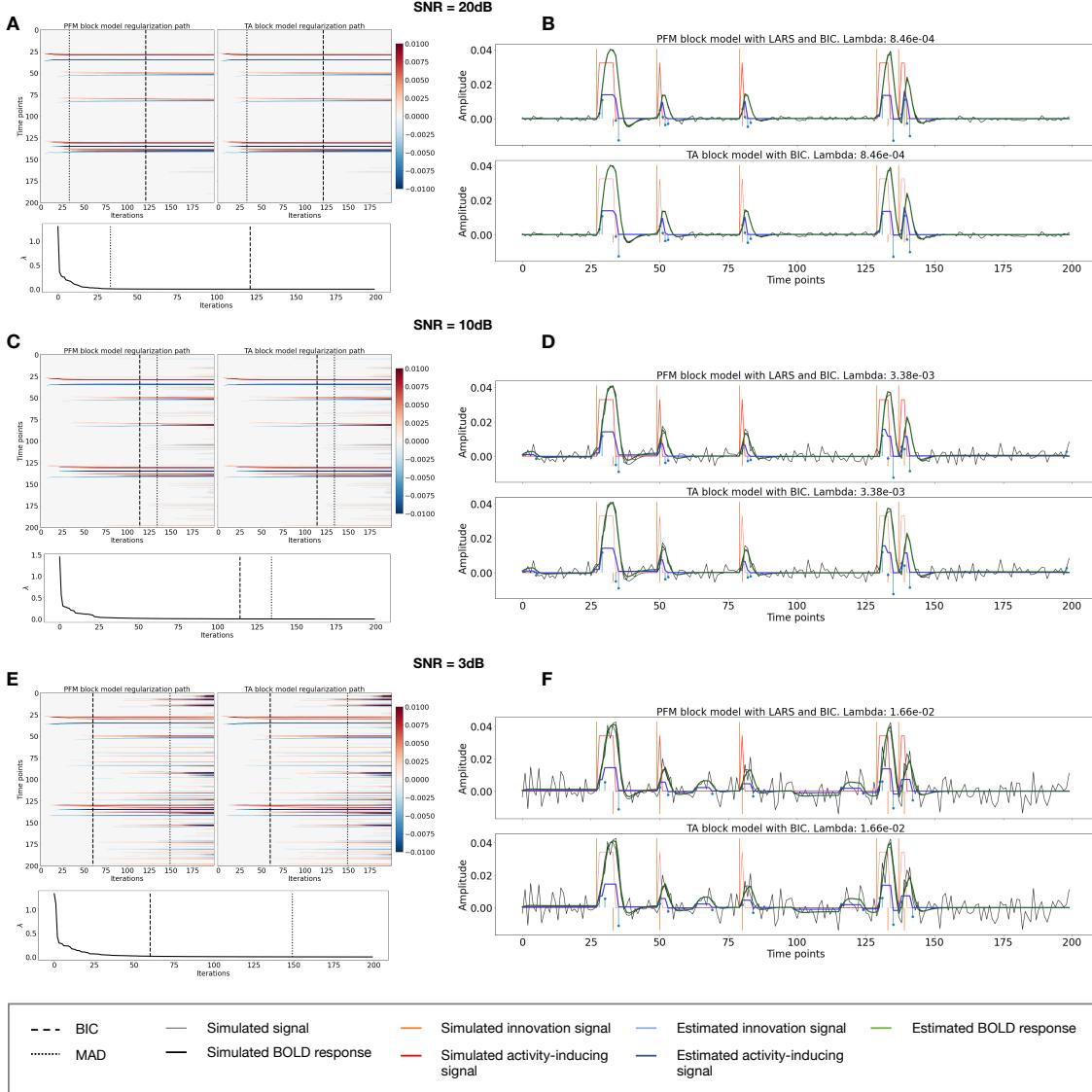


Figure S2: Block model simulations. (Left) Heatmap of the regularization paths of the innovation signal estimated with PFM and TA as a function of λ (increasing number of iterations in x-axis), whereas each row in the y-axis illustrates one time-point. Vertical lines denote iterations corresponding to the Akaike and Bayesian Information Criteria (AIC and BIC) optima. (Right) Estimated innovation (blue) and activity-related (green) signals when λ is set based on BIC. All the estimates are identical when compared between the PFM and TA cases, regardless of SNR.

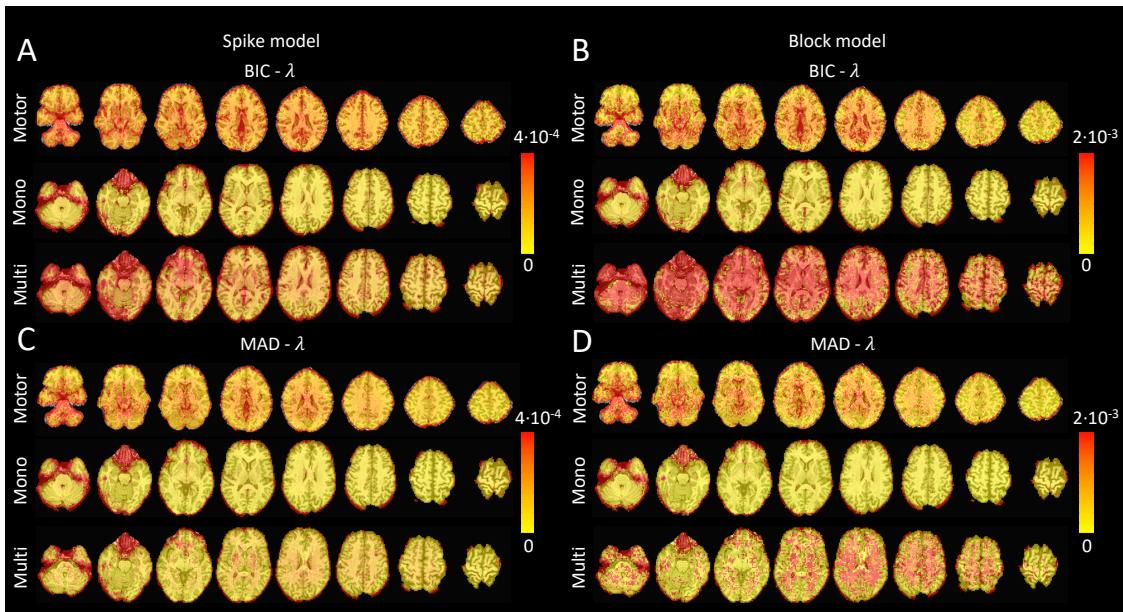


Figure S3: Values of λ across the different voxels in the brain used to estimate (A) the activity-inducing signal (spike model) and (B) the innovation signal (block model) with the BIC selection, as well as (C) the activity-inducing signal (block model) and (D) the innovation signal (block model) with a MAD-based selection. The λ maps are shown for the three experimental fMRI datasets: the motor task (Motor), the monoband resting-state (Mono), and the multiband resting-state (Multi) datasets.

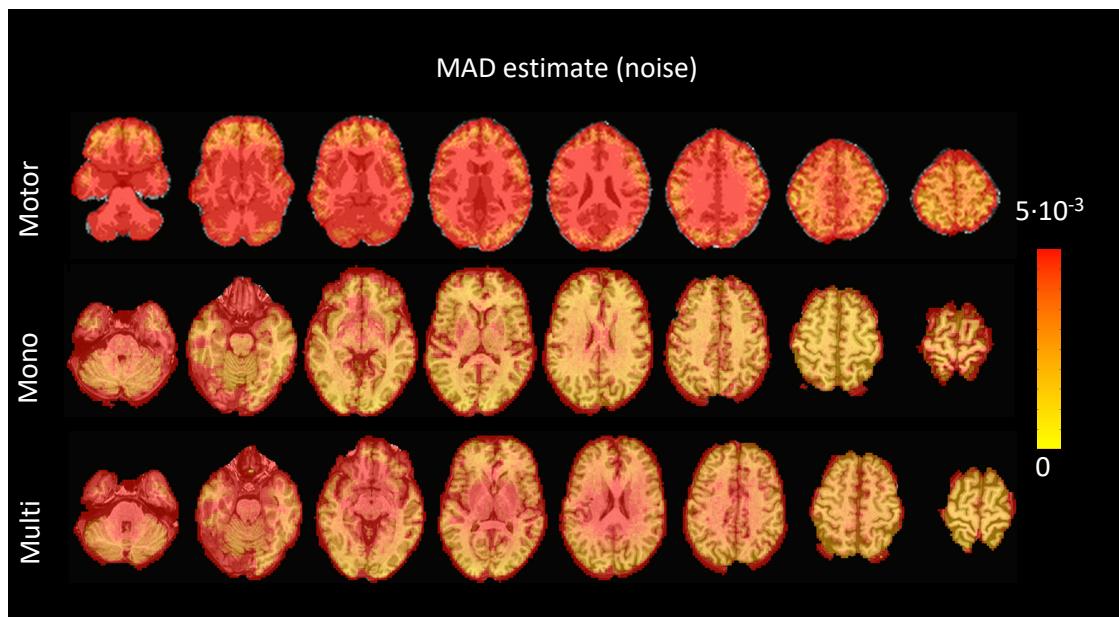


Figure S4: Values of the MAD estimate of standard deviation of the noise across the different voxels in the brain for the three experimental fMRI datasets: the motor task (Motor), the monoband resting-state (Mono), and the multiband resting-state (Multi) datasets.

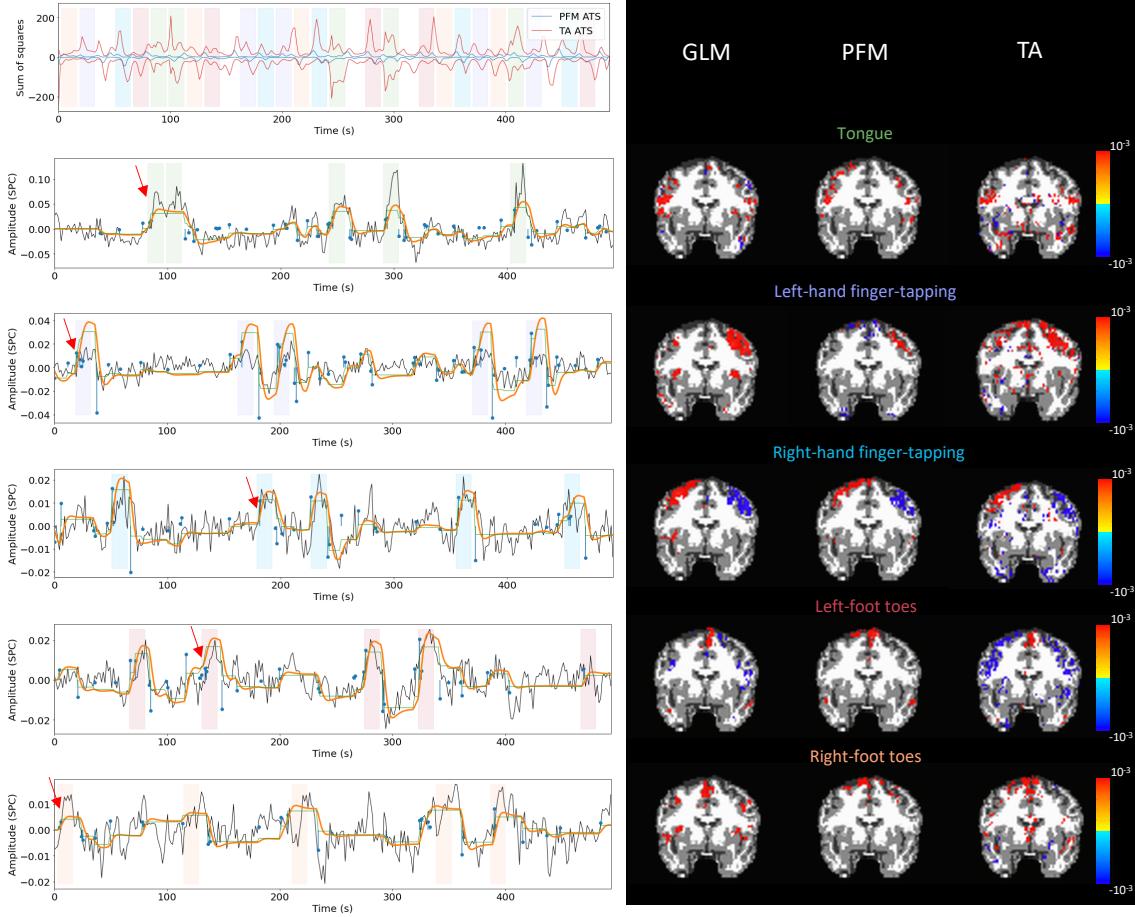


Figure S5: Activity maps of the motor task using a selection of λ based on the MAD estimate. Row 1: Activation time-series of the innovation signals estimated by PFM (in blue) or TA (in red) calculated as the sum of squares of all voxels at every timepoint. Positive-valued and negative-valued contributions were separated into two distinct time-courses. Color-bands indicate the onset and duration of each condition in the task (green: tongue, purple: left-hand finger-tapping, blue: right-hand finger-tapping, red: left-foot toes, orange: right-foot toes). Rows 2-6: time-series of a representative voxel for each task with the PFM-estimated innovation (blue), PFM-estimated activity-inducing (green), and activity-related (i.e., fitted, orange) signals, with their corresponding GLM, PFM, and TA maps on the right. The maps shown on the right are sampled at the time-point labeled with the red arrows and display the innovation signals at that moment across the whole brain.

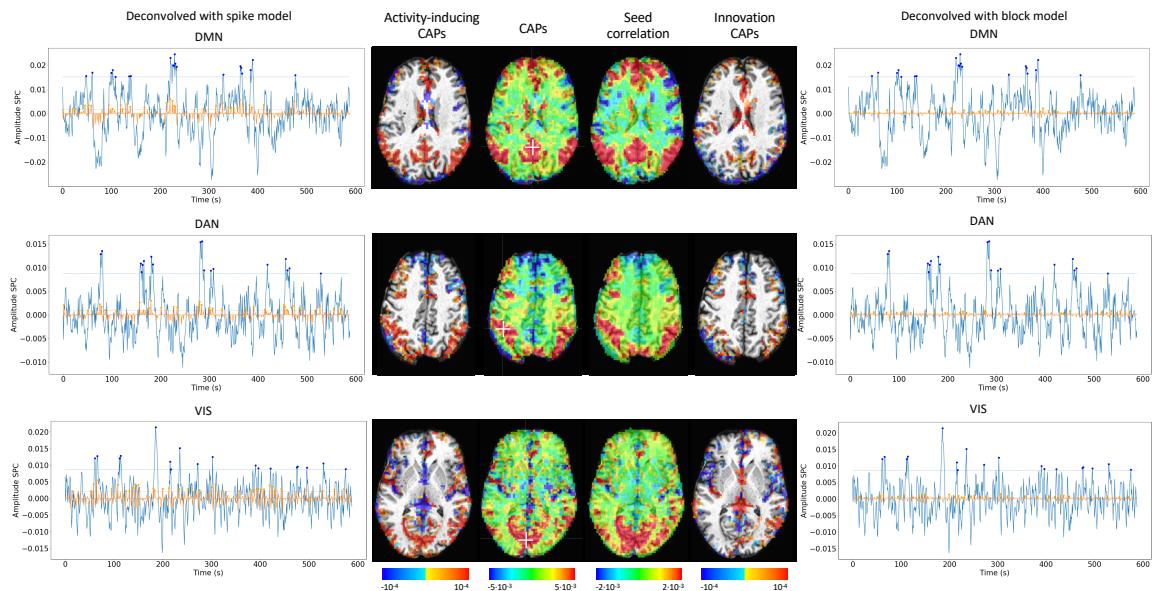


Figure S6: Activity-inducing CAPs (left) and innovation CAPs (right) obtained with the PFM-estimated activity-inducing and innovation signals respectively, using a MAD-based selection of λ . Time-points selected with a 95th percentile threshold are shown over the average time-series (blue) in the seed region (white-cross) and the deconvolved signal (orange). CAPs and seed correlation maps are illustrated in the center.