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Methods for cleaning the BOLD fMRI signal

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Abstract

Blood oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) has rapidly become a popular technique for the investigation of brain function in healthy individuals, patients as well as in animal studies. However, the BOLD signal arises from a complex mixture of neuronal, metabolic and vascular processes, being therefore an indirect measure of neuronal activity, which is further severely corrupted by multiple non-neuronal fluctuations of instrumental, physiological or subject-specific origin. This review aims to provide a comprehensive summary of existing methods for cleaning the BOLD fMRI signal. The description is given from a methodological point of view, focusing on the operation of the different techniques in addition to pointing out the advantages and limitations in their application. Since motion-related and physiological noise fluctuations are two of the main noise components of the signal, techniques targeting their removal are primarily addressed, including both data-driven approaches and using external recordings. Data-driven approaches, which are less specific in the assumed model and can simultaneously reduce multiple noise fluctuations, are mainly based on data decomposition techniques such as principal and independent component analysis. Importantly, the usefulness of strategies that benefit from the information available in the phase component of the signal, or in multiple signal echoes is also highlighted. The use of global signal regression for denoising is also addressed. Finally, practical recommendations regarding the optimization of the preprocessing pipeline for the purpose of denoising and future venues of research are indicated. Through the review, we summarize the importance of signal denoising as an essential step in the analysis pipeline of task-based and resting state fMRI studies.

Keywords

BOLD fMRI; Denoising methods; Motion artifacts; Physiological noise; Multi-echo; Phase-based methods

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Conflicts of interest

The authors have no conflicts of interest to declare.

1. Introduction

The functional magnetic resonance imaging (fMRI) signal is very noisy. The blood oxygen-level-dependent (BOLD) response induced by neuronal activity only represents a relatively small percentage of the variance of the signal (Bianciardi et al., 2009a). Non-neuronal contributions to the BOLD fMRI time series in a voxel include thermal noise inherent to the electrical circuits used for MR signal reception, instrumental drifts, artefactual signals due to hardware instabilities (e.g. spiking), signal changes due to head motion, as well as a multitude of physiological fluctuations of non-neuronal origin, including cardiac and respiratory noise, changes in arterial $C0_2$ concentration associated with varying respiration rate, vasomotion effects, and changes in blood pressure and cerebral autoregulation mechanisms (Murphy et al., 2013). The relative proportion of each component in the signal depends on the instrumentation, particularly the field strength, as well as on the neural and cerebrovascular physiology of each subject.

Since the value of the transverse relaxation rate (R2*) and its change (ΔR2*) increases with higher MR field strengths, the signal change of the BOLD response to neuronal activity also increases (van der Zwaag et al., 2009). Besides, continuous developments in hardware and acquisition sequences diminish the level of thermal noise and system-related artefacts in the signal. Nevertheless, these benefits do not always result in an increased contrast to noise ratio (CNR) of the signal since, in general, the sensitivity of the signal to non-neuronal physiological contributions also increases with higher field strengths. For example, physiological noise is generally proportional to the signal strength and when this noise contribution dominates, there is a plateau in the signal to noise ratio (SNR) at typical voxel resolutions for whole-brain imaging (Krüger and Glover, 2001; Triantafyllou et al., 2005; 2011; 2016). To benefit from the increased BOLD contrast at higher field strengths, the thermal noise should be larger in magnitude than non-neuronal physiological (i.e. cardiac and respiratory related) fluctuations so that the temporal signal to noise ratio of the signal remains within a linear regime as a function of the signal to thermal noise ratio. Reducing the voxel size is one way to achieve this (Bodurka et al., 2007). However, with increasing spatial resolution, the fMRI voxel time series potentially becomes more sensitive to motion-related fluctuations.

The contribution of non-neuronal fluctuations considerably affects the results of any task-based or resting state fMRI experiment. In task-based fMRI, there is an inherent risk of bias in the test statistics if non-neuronal fluctuations with a non-white power spectral density are not properly accounted for in the design matrix of the model and the estimation, or are previously reduced during preprocessing (Lund et al., 2006). This bias will reduce the sensitivity and specificity of detecting or characterizing the BOLD response to task-related neuronal activity (Friston et al., 2007). Although it is generally thought that task-based fMRI is sufficiently robust to non-neuronal fluctuations since the observed effect is typically measured as the average response to multiple trials, this is not certainly always the case since noise components might be correlated to the timing of the task, for instance head motion or physiological changes in cardiac rate or breathing due to the performance of the task. Non-neuronal fluctuations may also introduce common variance in the signals from different regions of the brain, thus confounding estimates of functional or effective

connectivity. This is particularly problematic in resting state fMRI where the assumption is that temporal correlation between the BOLD signals in different regions demonstrates they are functionally connected (Fox and Raichle, 2007). Therefore, non-neuronal fluctuations can increase the apparent functional connectivity between regions by introducing spurious common variance across time series. As such, the analysis of resting state data cannot benefit from an averaging process to remove these non-neuronal fluctuations as it is done in task-based fMRI. In resting state fMRI, the 'neuronal' reference model is based on the signal from a region of interest in case of seed correlation analysis, or a common fMRI signal within the components extracted by independent component analysis. Besides, although some studies have demonstrated the existence of BOLD-like response in resting state data (Petridou et al., 2013; Tagliazucchi et al., 2012; Liu and Duyn, 2013; Karahanoğlu and Van de Ville, 2015), it is still uncertain whether BOLD signal changes at rest achieve the same magnitude as in response to a task. In summary, cleaning the true neuronal-related BOLD activity from non-neuronal fluctuations is a challenging task in fMRI.

The aim of this work is to provide a comprehensive review of existing methods for cleaning the BOLD fMRI signal. Despite the multiple types of noise components, the review focuses on denoising the two types of non-neuronal fluctuations for which denoising methods have been mainly developed for, namely the effect of head motion and physiological noise fluctuations. However, it is necessary to emphasize that some approaches have been proven effective in reducing multiple types of noise because of the intrinsic relationships between noise sources (e.g. respiration and head motion) and because they do not assume any physiological or noise model, being sufficiently general in their scope. Furthermore, we also summarize denoising methods that benefit from the intrinsic characteristics of multi-echo fMRI and, those considering not only the magnitude of the initially complex fMRI signal, but also its phase, which has very valuable information regarding the physiology of the BOLD response and the noise components of the signal. A note regarding the often-controversial use of global signal regression is also given. Despite the enormous popularity of fMRI to study brain function, a consensus standard of the processing pipeline is yet to be reached. Therefore, we finally draw some guidelines regarding the preprocessing steps in order to leverage denoising methods. Compared with previous reviews, which focused more on a particular confound or type of fMRI data (e.g. Birn, 2012; Murphy et al., 2013, Power et al., 2015), our goal was to give a more methodological point of view about the operation of the different techniques, pointing out the advantages and limitations in their use. Furthermore, the focus was on methods developed for BOLD fMRI in humans and that typically perform any operation in the original subject's space (i.e. avoiding any spatial transformation to a standard template).

A point on nomenclature must be initially clarified. Multiple approaches are based on the extraction of reference signals characterizing noise fluctuations. We refer to these signals as nuisance signals or regressors and the process as nuisance regression since, in most cases, the final step in the denoising process is to include these signals as regressors in a design matrix that is fit to the fMRI voxel time series via an ordinary least squares estimator. Subsequently, to obtain the denoised signal, the variance explained by these regressors is subtracted from the data. This nuisance regression can be done prior to the final data analysis, and this will be typically identified as a preprocessing step. Alternatively,

the nuisance regressors can be included in the regression analysis along with regressors characterizing the hypothesized neuronal-related BOLD response in order to account for their variance in the fitting, and subsequently during statistical inference by properly adjusting the number of degrees of freedom used to fit the signal.

2. Denoising motion-related noise

2.1. Origin of motion-related noise

Head movements considerably influence the quality of the fMRI signal, either during resting state or while performing a task. Compensating the effects of head movement has always been an important issue in fMRI data analysis; see the seminal works by Hajnal et al. (1994) and Friston et al. (1996). In task-based fMRI, the main concern of head motion is when head movements may correlate with experimental tasks (e.g. during overt speech or swallowing), hindering the ability to differentiate BOLD fMRI from subject motion artefacts despite averaging the response across multiple trials. Task-correlated motion is more problematic in block designs than in event-related designs due to the delay of the haemodynamic response with respect to the rapid effect of motion in the signal (Barch et al., 1999; Birn et al., 1999; Bullmore et al., 1999; Johnstone et al., 2006; Morgan et al., 2007; Oakes et al., 2005; Soltysik and Hyde, 2006; Xu et al., 2014). In resting state fMRI, even small amounts of motion or micromovements within and between scans can significantly confound estimates of functional connectivity between voxel time series. Unlike task-based fMRI, motion artefacts in resting state cannot be suppressed by averaging. Motion-induced signal fluctuations can cause both increases and decreases in the correlations between voxel time series depending on the waveforms that motion generates in each voxel signal. Head motion creates spurious correlations at the subject-level that challenge the interpretation of functional connectivity studies comparing populations with different proneness to head movement. For instance, it has been observed that motion adds spurious variance that is more similar between nearby voxels than between distant voxels, causing distance-dependent modulation of signal correlations (Power et al. 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012).

The origin of motion-related signal changes in fMRI can be described in terms of three interrelated effects. First, the amplitude of the signal in a voxel is directly proportional to its net magnetization S_0, which in turn depends on the density of protons within the voxel at given scan. Hence, any alteration in tissue composition within the voxel due to head motion will cause a change in S_0 and thus in the signal. Second, the number of excited spins depends on the position of the voxel during a given scan, but also on the position in previous scans. Generally, it is assumed that S_0 in a voxel is at steady state, and that is the reason why the initial scans of an acquisition showing transient effects in amplitude are typically discarded until magnetization achieves steady state. However, movement of the head alters the timing between successive excitations experienced by spins in the voxel, particularly if movement occurs across the slice plane, generating spin history artefacts in the signal that can last for several scans until steady state magnetization is recovered again (Beall and Lowe, 2015; Bhagalia and Kim, 2008; Friston et al., 1996; Muresan et al., 2005). Spin history artefacts can be spatially variable, e.g. head nods affect voxels in frontal areas

selectively. If due to large head movement, a brain region experiences successive excitations, it implies that another region has not been excited, introducing spatially correlated effects in the signal that may be visible as banding patterns in the image (e.g. see Power et al., 2016). Third, movement of the head will make the magnetic field become inhomogeneous since shimming calculations were obtained for a particular head position prior to acquisition. This changes the spatial distribution of the local magnetic susceptibility gradients, and exacerbates distortions and signal dropouts in locations prone to these effects (Jiang et al., 1995). In general, the effect of head motion is predominantly seen in voxels at the edges of the brain, although it can also be particularly severe in voxels lying close to a tissue boundary due to the differences in proton density and relaxation parameters across brain tissues (Jo et al., 2010; Lemieux et al., 2007; Patriat et al., 2015).

2.2. Reducing motion-related effects and related fluctuations

Volume registration is generally included as one of the initial steps in data preprocessing to reduce the influence of head motion in the signal. Volume registration consists of aligning each scan acquired in time to a registration base from the same run or other run, ideally a volume with the least amount of motion artefact (e.g. see the MIN_OUTLIER option in afni_proc.py) or the voxel-wise average or median volume computed across the whole time series, often after an initial coarse realignment step. To simplify the computation of the realignment transformations, it is typically assumed that head motion is a rigid body process and, thus, computing an affine transformation including 6 directional parameters (i.e. 3 translation and 3 rotation) is sufficient to capture it (Cox and Jesmanowicz, 1999; Friston et al., 1995; Jiang et al., 1995). Most subject-level registration algorithms adopt a volumetric registration strategy, applying a single correcting transformation to all slices at once. Certainly, this is an oversimplification of the problem since as a subject moves, each slice may be transformed differently. As a result, motion-related artefacts may impact all slices of an image, or only some of them. Slice-to-slice registration approaches have been recently revisited to correct for head motion in a more refined manner and, hopefully, more effective manner than volumetric approaches, particularly using an anatomical scan to help in the registration (Bhagalia and Kim, 2008; Ferrazzi et al., 2014; Kim et al., 1999). Slicewise motion correction approaches are becoming increasingly effective in compensating within volume motion (Beall and Lowe, 2014; Chen et al., 2015; Zotev et al., 2012). However, it is important to understand that registration cannot correct the data to be as if the motion had never occurred. In fact, volume registration can create spurious activations in the absence of subject motion (Freire and Mangin, 2001; Grootoonk et al., 2000).

Therefore, even after volume registration, it is usually required to compensate for motion-related signal changes remaining in the data. The most common motion correction approach is to add the time series of the 6 estimated realignment parameters as nuisance regressors in a regression model in order to account for their explained variance. To further remove spin history related aspects of motion-related artefacts, Friston et al. (1996) proposed a nonlinear expansion of the realignment parameters including its temporal derivatives and corresponding squared regressors. Sets of 12, 24 or 36 motion-related regressors, incorporating the original time series, their squared time series, plus one or two temporal shifts, or new motion ‘fingerprint’ regressors have also been employed (Chai et al.,

2012; Friston et al., 1996; Lemieux et al., 2007; Power et al., 2012; Power et al., 2014; Satterthwaite et al., 2013; Van Dijk et al., 2012; Wilke, 2012; Yan et al., 2013a). Explaining additional variance using more motion-related regressors must be balanced against the loss of degrees of freedom since it is not possible to know whether all motion related effects in the signal have been removed, or whether neuronal-related fluctuations are also started to be removed.

In practice, head jerks produce the most problematic signal changes. These head movements generate large changes in image intensity at the time of the motion with varying waveforms that may not be properly explained by the realignment parameters, and will therefore bias any parameter estimate. To reduce such residual abnormalities in the data, a popular approach is to censor image volumes acquired during periods of high-motion, i.e. remove these time points entirely. Censoring is also known as scrubbing (Carp, 2013; Jones et al., 2010; Kennedy and Courchesne, 2008; Power et al., 2012, 2013, 2014; Siegel et al., 2014), and is equivalent to adding scan nulling regressors in the model (Lemieux et al., 2007; Satterthwaite et al., 2013; Yan et al., 2013a). Another common alternative is to interpolate the data between the corrupted volumes, for example using the ArtRepair software (Mazaika et al., 2009).

The time points affected by large head motion (or severe artefacts) can be identified based on traces of head motion derived from the relative head displacement between consecutive time points of the realignment parameters, such as the Euclidean Norm (Jones et al., 2010) or the Framewise Displacement (FD) (Power et al., 2012). Decisively, multiple definitions of these metrics have been proposed in the literature with the same name, and are available across softwares (Yan et al., 2013a, Power et al., 2015). Both translation and rotation parameters must be considered to compute head motion metric, instead of only the 3 translation or the 3 rotation parameters (Wilke, 2012; 2014). Although the different definitions of the traces are highly correlated, their magnitude differ depending on the TR of acquisition, and can be influenced by how data is processed (e.g. data interpolation) prior to realignment. Therefore, setting up a threshold to identify corrupted data segments must be uniquely done and reported for each dataset (Power et al., 2015). Furthermore, an important question is how many volumes exhibit motion-related signal changes and should be censored since spin history artefacts will manifest as a long period of a dephased signal, i.e. the T2* signal is lost, and they can last up to 8 or 10 s after motion. Therefore, as an addition or alternative to metrics based on the realignment parameters, a criterion for deciding time frames to be censored or interpolated can be formulated from the data itself, for example as it is measured by the Derivative or root mean square VARiance over voxelS (DVARS) (Smyser et al., 2010), based on fractions of the brain appearing as temporal outliers (as can be done with afni_proc.py), or detecting time points with larger signal changes than physiologically plausible according to a BOLD response model (Tierney et al., 2016).

Several points must be taken into account if censoring is used to reduce the impact of motion-contaminated data. First, censoring results in a reduction in the temporal degrees of freedom. At a given threshold, the number of censored time points will increase in subjects who move more, leading to fewer degrees of freedom in these subjects. This could lead to biases that covary with factors of interest in group comparisons. Second, synthetic data

and temporal discontinuities are introduced by data interpolation and censoring, respectively, disrupting the temporal correlation of the signal. The effects of temporal interpolation depend on the duration of the censored segment, the autocorrelation of the signal, as well as the type of interpolation, such as linear, Fourier, wavelets or splines interpolations. As a consequence, the use of censoring and data interpolation must be addressed carefully, for instance by setting up a maximum number of interpolated or censored volumes and/or balancing the amount of censored volumes across populations in a group comparison, as these approaches may bias the results in task-based fMRI and resting state studies.

A drawback of censoring or despiking approaches applied in the time domain is that they can only isolate high frequency events such as step changes in signal intensity and large amplitude spikes. However, they find difficulties in correctly identifying prolonged and step-like motion-related signal changes due to spin history artefacts. To overcome this limitation, Patel et al. (2014) proposed a wavelet-based despiking algorithm that searches for chains of maximal and minimal wavelet coefficients across multiple scales or frequencies, being able to identify both high and low frequency non-stationary events. Furthermore, since it is applied to all voxels independently, it tunes its operation to only those voxels where motion artefacts are present, instead of affecting globally as with censoring or scan-nulling regression. This procedure can also be used to estimate the effective degrees of freedom of the raw data and after denoising (Patel and Bullmore, 2015).

Importantly, compensation of head motion of fMRI data requires measurements with higher temporal resolution than the fMRI sampling rate. Otherwise, compensation of effects due to head motions occurring at shorter time scales that may only impact a subset of slices would be limited. In that sense, the high temporal resolution of external optical tracking systems (Schulz et al., 2014; Speck et al., 2006; Todd et al., 2015) or the use of dedicated sequences with navigators echoes or active markers (Hu and Kim, 1994; Lee et al., 1996; Muraskin et al., 2013; Pfeuffer et al., 2002; White et al., 2010) can be useful for prospective motion correction (Zaitsev et al., 2016). The extra information can also be used retrospectively. Unfortunately, these advanced technologies are not commonly available at all sites during fMRI acquisitions, although most modern scanners include a method for semi-prospective head motion correction for fMRI that applies volumetric registration shortly after the acquisition of the volumes and corrects the current axes of the acquisition coordinate system (Thesen et al., 2000). In the case of simultaneous EEG and fMRI acquisitions, an MR-compatible EEG cap can be used as a sensitive motion detector (Zotev et al., 2012). If EEG data is concurrently acquired during the fMRI experiment, two nuisance regressors describing rotational head movements can be obtained with millisecond temporal resolution based on an automatic identification of motion-related independent components of the EEG data, and then regressed out from the raw fMRI data before any preprocessing (Wong et al., 2016a, 2016b; Zotev et al., 2012). This technique, known as EREMCOR, is able to remove within-volume motion effects as well as slow motion-related signal drifts that may occur during the entire acquisition. In addition, since E-REMCOR regressors are solely derived from the EEG data, they are not affected by any artefact that may be present in the fMRI data (Zotev et al., 2012).

Finally, it should be recognized that the correction of motion effects lacks a ground-truth validation framework which motion-compensation algorithms can be benchmarked to. In that sense, recent efforts have focused on the development of techniques that can model or acquire motion corrupted fMRI data with a precise knowledge of the amount and type of motion at the slice acquisition level. SimPACE is a strategy that modifies the pulse sequence by altering the MR gradients on-the-fly independently for each slice according to pre-defined sequence of head movements (Beall and Lowe, 2014). Initially evaluated in cadaver data, SimPACE has been recently used along with individualized 3-D printed headcases in order to obtain fMRI data with minimal motion in healthy subjects. These “motion-free” datasets can serve as reasonable benchmark for evaluating motion-correction algorithms (Tambini et al., 2016). In addition, SimPACE has been used to evaluate the performance of SLOMOCO, a retrospective motion-removal technique that estimates slice-wise rigid body motion parameters that are subsequently regressed out from the signal according to a second-order voxel- and slice-specific motion regression model (Beall and Lowe, 2014). The combination of SimPACE and SLOMOCO was proven useful to demonstrate that commonly used motion metrics based on volumetric motion parameters, such as framewise displacement (Power et al., 2012), might not display all motion effects present in the fMRI data, calling for the use of slice-wise motion-related metrics (Beall and Lowe, 2014).

3. Non-specific data-driven denoising methods

Nuisance regressors can also be derived in a data-driven way with the motivation of accounting for multiple types of noise sources, from motion-related effects and artefacts to non-neuronal physiological fluctuations. Regarding motion-related effects, data-driven approaches may exhibit greater sensitivity to account for slicewise motion than nuisance regressors derived from the realignment parameters with TR resolution. Furthermore, data-driven nuisance regressors may capture better the spatial heterogeneity of noise across tissues. In addition, they do not typically make any assumption about the relationship between the source of noise and the resulting change in the MR signal. For instance, they can reduce motion-related signal changes that might not be linearly related to the rigid-body realignment parameters or their second-polynomial expansion.

Nuisance regressors can be generated from tissues or regions. Considering the average signals of white matter (WM) and ventricular cerebrospinal fluid (CSF) tissues as nuisance regressors has become fairly common in resting state and task-based fMRI approaches (Anderson et al., 2011; Hallquist et al., 2013; Jo et al., 2010, 2013; Power et al., 2012; Weissenbacher et al., 2009; Yan et al., 2013a). More elaborated approaches have also considered nuisance regressors defined from soft tissues (Anderson et al., 2011) or the edges of the brain (Birn et al., 1999; Patriat et al., 2015). In some cases, the temporal derivatives of each tissue-based regressor are also included (Fox et al., 2005; Power et al., 2014; Satterthwaite et al., 2013) or are shifted to maximize the impact of denoising (Anderson et al., 2011). Eroding the masks at the fMRI resolution is crucial to reduce partial volume effects from neighbouring tissues. For example, WM-based regressors can account for variance in GM voxels if not eroded, mostly due to partial volume effects. Similarly, nuisance regressors must be defined prior to any spatial smoothing to avoid mixing data

from different tissue types and exacerbate partial volume effects (Jo et al., 2010, 2013; Power et al., 2016).

A limitation of considering the average signal across tissues is that they cannot capture any spatial variability of the noise that could exist across the entire span of the mask. To account for that, nuisance regressors can be computed from masks restricted to a small local neighbourhood of WM voxels around each voxel as in ANATICOR (Jo et al., 2010; 2013). In ANATICOR, the rationale of adding local WM signals among the nuisance regressors is to remove artefacts with very localized spatial scale that affect the fMRI time series, e.g. due to hardware-induced artefacts resulting from faulty head channel coils, errors in the calibration of sensitivity profiles (Jo et al., 2010), or small local changes in the local magnetic field resulting from movement (Jo et al., 2013). In terms of computation, since the local WM regressor is a function of voxel location, a voxel-dependent regression approach is required to orthogonalize the data with respect to the nuisance regressors, as it is implemented in the 3dREMLfit, 3dTfitter and 3dTproject programs in AFNI.

3.1. Denoising methods based on principal component analysis (PCA)

Defining multiple spatially uncorrelated nuisance regressors based on the principal component analysis (PCA) decomposition of voxels where no BOLD fMRI signals of neuronal origin are expected to originate is another popular approach account for the spatial and temporal variability of the noise sources. The widely-used CompCor approach (Behzadi et al., 2007; Muschelli et al., 2014) defines multiple nuisance regressors from the principal components (PCs) of voxels within WM and CSF in the ventricles, rather than using the average WM and CSF signals. CompCor can account for cardiac and respiratory fluctuations (Behzadi et al., 2007) as well as the effects of head motion (Muschelli et al., 2014). An important question is how many principal components (PCs) must be considered in the model. Muschelli et al. (2014) examined two different strategies to define the sets of principal components (PCs): either the original anatomical CompCor approach that considers a fixed number of PCs from WM and also from CSF (e.g. 5 WM and 5 CSF PCs), or a data-specific criterion that considers enough PCs to explain a given percentage of the variance of the voxels (e.g. 50%) in each tissue. In practice, the second strategy shows better performance since it can adjust the number of PCs to the quality of the voxel time series. In addition, more spatially coherent PCs are generally required to model the variance of WM voxels than the variance of CSF voxels. Furthermore, both strategies outperform the use of average WM and CSF signals as nuisance regressors. Importantly, censoring seems to be unnecessary or even be detrimental when CompCor approaches are used for denoising resting state data (Muschelli et al., 2014). In general, these observations were obtained regardless of the level of motion across subjects (i.e. low-motion and high-motion subjects) as well as regardless of the spatial location of the ROIs (e.g. regions close to the outer edge of the brain vs. inner cortical and subcortical areas), with further improvements in functional networks comprising long-range connections than in those with short-range connections (e.g. the default mode network vs. the motor network) (Chai et al., 2012; Muschelli et al., 2014).

Nuisance regressors can also be determined by the PCs of voxel time series located on the outer edges of the brain (Birn et al., 1999; Patriat et al., 2015) in order to account for motion-related signal changes, respiration-induced fluctuations and system artefacts that are typically well represented in these voxels. Importantly, it is recommendable that the mask of the brain's edge voxels is defined considering both functional and anatomical within-brain masks in order to minimize the possibility of removing any potential true neuronal activity-related BOLD signal of interest in voxels affected by susceptibility artefacts and signal dropouts in the functional image (Patriat et al., 2015). In resting state data, regression models including 6, 12 or 24 principal components of edge brain voxels outperformed other comparable models based on the realignment parameters, explaining more motion-related variance, reducing DVARS and increasing temporal SNR. In general, these results were observed regardless of the use of censoring or global signal regression (Patriat et al., 2015).

To avoid the dangers of including BOLD signals in tissue-based or edge-based regressors, motion-based nuisance regressors can also be obtained by creation of motion-simulated time series, wherein a base volume is transformed according to estimated subject motion. An additional time series dataset can be made by subsequent registration of the simulated dataset (Patriat et al., 2016). From these datasets, PCs over the whole brain could be extracted from either the simulated dataset, the registered version, or both, after spatial catenation. Using 12 such components has shown to explain more variance than the standard 6 realignment parameters and their derivatives. Furthermore, either of the two datasets could be applied directly as voxelwise regressors. If one wanted to combine the 12 simulated components with those standard 12 components, the standard realignment components could be projected out of the simulated time series before PCA is computed (Patriat et al., 2016).

Several methods based on PCA have also been specifically designed for denoising task-based fMRI data assuming a linear relationship between the task model and the neural response. In Kay et al. (2013), the denoising approach of GLMdenoise proposes to perform PCA on task-unrelated voxels identified after an initial model fit. Cross-validation of the task-related response is used to identify the optimal number of PCs, which are then used as nuisance regressors in a second model fit. Importantly, in task-based fMRI the optimal number of PCs not only depends on the magnitude of the noise, but also on the magnitude of the task-related signals and the correlation between the noise and the task-related signals (e.g. in presence of task-correlated motion). A limitation of this approach is that, by defining a pool of task-unrelated voxels, there exists an inherent risk of selecting false negative voxels within the pool and that the nuisance regressors are able to explain task-related activity. In fact, this problem also exists in other approaches defining regressors from voxels within tissue specific masks, as in CompCor (Behzadi et al., 2007), or whole-brain masks (Soltysik et al., 2015). Therefore, orthogonalizing the task-unrelated voxel time series (Bianciardi et al., 2009b; de Zwart et al., 2008) or the principal components with respect to the task-related model (Soltysik et al., 2015) is crucial to circumvent this potential problem.

The pool of task-unrelated voxels can alternatively be defined as those voxels that do not respond to the task after an initial model fit, and also do not exhibit a significant correlation with the average signal of the active voxels during resting state (de Zwart et al., 2008; Bianciardi et al., 2009b). The rationale of this approach is that spontaneous

fluctuations during the resting state can serve as a valid approximation of all sources of signal variance that may obscure task-related activity, not only including motion-related signals and physiological cardiac and respiratory fluctuations but also signals of neuronal origin that account for trial-by-trial variability in the evoked BOLD responses (Fox et al., 2006). The use of this approach is limited by the fact that resting state data must be acquired in addition to the task-fMRI data. Furthermore, it assumes that the spurious spontaneous fluctuations in the active voxels during the task can be modeled from voxels that are functionally connected during rest, but are not connected during the task. This might not be a valid assumption if spontaneous fluctuations in the active and task-unrelated voxels have different signal sources, or if the structure of the network change between the two experimental conditions (i.e. during rest and during the task). Also, care must be taken at the time of defining the initial model or choosing the significance threshold in order to avoid selecting false negatives within the set of unrelated voxels. It is certainly possible that voxels belonging to the same functional network during rest are also functionally connected during the execution of a task (Biswal et al., 1995; Smith et al., 2009); they might exhibit a BOLD response to the task, although not sufficiently significant in statistical terms.

3.2. Denoising methods based on independent component analysis (ICA)

Alternative strategies for denoising fMRI data can also exploit independent component analysis (ICA). Once the ICA is computed, the basis of these denoising approaches is to first distinguish between independent components (IC) related to neuronal-related BOLD signal and ICs related to noise sources, and then remove the latter before reconstructing the dataset (Beckmann, 2012; McKeown et al., 2003). Note that this way of operating would also be appropriate if the data is decomposed into components based on linear PCA (Thomas et al., 2002) or nonlinear kernel PCA (Abrahamsen and Hansen, 2011; Rasmussen et al., 2012; Song et al., 2014). However, PCA-based methods have become less popular for the purpose of denoising except, as described above, for the definition of regressors based on the principal components.

In practice, manual classification of the ICs is very time consuming, difficult to reproduce and requires expertise (Kelly Jr. et al., 2010). Therefore, several procedures have been proposed for assisting automated classification, which mainly differ in the algorithms used for supervised classification (and if necessary feature selection), the number and definitions of the spatial and temporal features used in the classification, as well as the type of fMRI data they are optimized to work with, either task-based, resting state, or both (Beall and Lowe, 2007; Bhaganagarapu et al., 2013; De Martino et al., 2007; Douglas et al., 2011; Formisano et al., 2002; Griffanti et al., 2014; Kochiyama et al., 2005; Liao et al., 2006; Perlbarg et al., 2007; Pruim et al., 2015a; 2015b; Rummel et al., 2013; Salimi-Khorshidi et al., 2014; Sochat et al., 2014; Soldati et al., 2009; Storti et al., 2013; Sui et al., 2009; Thomas et al., 2002; Tohka, et al., 2008; Wang and Li, 2015, Xu et al., 2014).

Regarding the classifier, linear discriminant analysis, K-NN, clustering methods, naïve Bayes, (sparse) logistic regression, support vector machines, decision trees, random forests, or even ensemble of classifiers, have been proposed. For the sake of denoising, the classifier only requires to distinguish between two classes: the neuronal-related BOLD components to

remain, versus the noise components to remove. Often, multi-class classification may also be useful to differentiate between different types of artefacts and noise (e.g. De Martino et al., 2007). Regarding the features, temporal features derived from IC time series can include: the fraction of spectral power above a certain frequency (e.g. 0.1 Hz in resting state, or the frequency of stimulus frequency in a task), the distribution across frequency bands, the correlation with task-related regressors or with the realignment parameters or tissue-based signals, the temporal smoothness of the IC time series, its autoregressive properties, histogram-based statistics, the presence of spikes, or descriptors of neural-like BOLD activity. On the other hand, spatial features derived from thresholded or non-thresholded IC maps might include: clusters' sizes and distribution, spatial frequency, entropy and smoothness, as well as fractions of the IC map that occur in GM, the edges of the brain, WM, ventricular CSF, major blood vessels and sinuses. The number of features is highly variable across algorithms, ranging from up to 246 features in Sochat et al. (2014) or over 180 features in FIX-ICA (Salimi-Khorshidi et al., 2014) so that the classifier is able to generalize well across multiple types of noise components, to few features with the aim of making the approach be more robust and specific to a certain type of components, for instance 4 features are used in ICA-AROMA with an emphasis in reducing motion effects (Pruim et al., 2015a). Furthermore, spatial ICA is in general preferred over temporal ICA decompositions since there is more statistically meaningful information about the degree of autocorrelation, independence and sparsity of the data components in the spatial domain than in the temporal domain (Calhoun et al., 2013; Daubechies et al., 2009). Convergence of the algorithm in temporal ICA requires a large number of observations relative to the number of voxels, which can be achieved by accelerating the sampling rate or limiting the spatial coverage of the analysis (Smith et al., 2012). Even so, temporal ICA has been used in Beall and Lowe (2007) for isolating physiological noise components.

Recent work on ICA-based approaches for denoising has focused on designing classifiers with good generalization properties across multiple datasets so that no re-training of the classifier is required when the method is applied for denoising new datasets (Bhaganagarapu et al., 2013; Pruim et al., 2015a). However, it is important to understand that the classification accuracy could diminish if the characteristics of the data substantially deviate from the training data (e.g. in case of limited FOV, very short TR, rare artefact types). When there is automatic classification without expert supervision, it is thus advisable to choose conservative thresholds to reduce the risk of removing signal components, as well as to perform noise removal in a non-aggressive manner (i.e. to include both the BOLD-like and noise components in the regression model during the reconstruction of the signal) (Salimi-Khorshidi et al., 2014; Sochat et al., 2014). Performing a nonaggressive reconstruction is also a good compromise because the time courses of the components are not necessarily orthogonal and the ICA decomposition might not be able to completely separate the neuronal-related BOLD signal from the noise into different components. For instance, it has been suggested that spatial ICA cannot completely separate physiological noise components from neuronal-related BOLD components, and it is advisable to correct for physiological noise prior to ICA decomposition (Beall and Lowe, 2010; Birn et al., 2008).

Whereas most ICA procedures operate at the subject-level for denoising, it has also been suggested that identifying the artefactual components based on group-ICA and then computing the individual ICs using the remaining non-artefact ICs might be a better approach for denoising. This strategy might be particularly recommended if the goal is to reveal resting state functional networks across subjects (Du et al., 2016; Wang and Li, 2015). Furthermore, it is important to consider that in case of group studies comparing patients and healthy controls (or two populations), the classifier must be trained in a subset of the healthy controls, rather than on an equal number of patients and controls (Griffanti et al., 2016).

Two additional methodological points must be considered in case of denoising with ICA-based methods. First, the relative percentage of neuronal-related BOLD and noise components depends on the number of components of the ICA decomposition, ultimately influencing the efficacy of denoising. For example, at lower orders both BOLD and noise signals are likely to be mixed in the same component. In practice, it has been shown that the number of noise ICs is lower or approximately equal than that of neuronal-related BOLD ICs for low order ICA, but the former are about twice larger in case of high order ICA. Similarly, ICs describing a single functional network can split into several ICs at increasing orders (Abou Elseoud et al., 2011; Wang and Li, 2015). In theory, the number of ICA components could be estimated based on the space spanned by the non-thermal components of the data. Unfortunately, this is difficult task since the dimension of the data is first reduced via principal component analysis. A practical solution proposed in Tohka et al., (2008) is that if all noise components are removed, estimating again the optimal number of ICs with the denoised data should yield an equal or very similar number as the number of BOLD ICs that were kept. Therefore, if the new estimate substantially differs, it means that there could be hidden components that were revealed only when the overlying noise was reduced. Since some of these new components could be related to noise, reiterating the process might thus improve the quality of the signal in some cases (Tohka et al., 2008). Second, the ICA algorithm relies on a random initialization, and therefore the IC maps and time series will slightly differ across multiple runs of the algorithm (see Remes et al., 2011 and references therein). Hence, the classification may also change and in so the denoising performance. Fortunately, in practice, it has been observed that this variability is not very detrimental in terms of denoising, particularly for group studies (Tohka et al., 2008).

Finally, instead of aiming at the classification of the components, a motion-correction ICA method has been proposed for volume registration and isolating motion-related signal effects based on a different perspective that directly works on the difference between the entropies of the fMRI data and the spatial ICs (Liao et al., 2005; 2006).

4. Denoising physiological-related noise: cardiac, respiration and end-tidal CO_2 fluctuations

4.1. Origin of physiological noise fluctuations

Non-neuronal physiological fluctuations account for a percentage of the signal variance of the fMRI signal that is often comparable to that of the evoked BOLD response in task-based studies, and neuronal-related fluctuations observed at rest. Despite efforts in minimizing

head movements and reducing movement-related signal changes, pulsatility of blood flow in the brain and respiration-induced changes always exist in the fMRI signal. Cardiac pulsatility generates small movements in brain tissue as well as inflow effects in and around vessels. Therefore, the noise introduced by cardiac pulsations is often localized in tissue regions close to large arteries and draining veins, such as the sagittal sinus or the circle of Willis, as well as in the edges of the brain and sulci (Bhattacharyya and Lowe, 2004; Dagli et al., 1999; Glover et al., 2000). Additionally, thoracic movements during breathing result in respiratory-dependent changes in the magnetic field in the head volume that produce a shift in the phase of the MR image (Brosch et al., 2002; Raj et al., 2000; 2001; van de Moortele et al., 2002; Wowk et al., 1997). Small movements of the head due to breathing may also introduce spin history artefacts (Friston et al., 1996) and changes in phase information (Hagberg et al., 2008; 2012; Hu and Kim, 1994; Petridou et al., 2009). Depth and rate of respiration can also cause changes of end-tidal CO_2 ($P_{ET}CO_2$) (Birn et al., 2006; Chang and Glover, 2009b; Wise et al., 2004). Furthermore, both cardiac pulsations and respiratory cycles lead to bulk motion of large brain regions, such as the diencephalon or the brainstem (Brooks et al., 2013; Harvey et al., 2008), which will produce brain deformation, alter CSF flow and increase cranial pressure in the ventricles and nearby regions (Greitz et al., 1993; Klose et al., 2000; Piché et al., 2009). In addition, pulsations occurring at very low frequencies (0.001–0.073 Hz) have been found to be also a mechanism for CSF pulsations (Kiviniemi et al., 2016). The combination of these physiological effects will cause changes in the net magnetization in brain tissue due to partial volume effects, thereby generating subtle changes in the MR signal. Although respiration-induced fluctuations tend to span the entire brain, localized respiratory effects can thus also be observed in many regions of the brain due to interaction between respiration, cardiac pulsatility and blood pressure (Glover et al., 2000). It has been hypothesized that cardiac and respiratory fluctuations affect different vessel systems. Whereas cardiac-induced artefacts mainly occur in the arterial vascular system, breathing-related signal changes mainly occur in the venous vascular system (Windischberger et al., 2002).

The primary cardiac-related and respiratory-related components of the fMRI signal typically fluctuate at about 1 Hz for cardiac and 0.3 Hz for respiration. These frequencies are relatively high with respect to the spectral signature of standard evoked BOLD responses, where the hemodynamic process acts as a low pass filter with cutoff frequency approximately below 0.25 Hz (Friston et al., 2007). These frequencies are also higher than frequencies of interest in resting state studies, typically below 0.1 Hz (Fox and Raichle, 2007), even though there is increasing evidence that relevant neuronal-related fluctuations might also occur at higher frequencies (Boubela et al., 2013; Boyacioğlu et al., 2013; Chen and Glover, 2015; Kalcher et al., 2014; Niazy et al., 2011). Based on these frequency values, the Nyquist criterion establishes that the TR must be higher than 0.6 Hz (i.e. TR < 1.6 s) and 2 Hz (i.e. TR < 0.5 s) so that there is no aliasing of the first respiratory and cardiac harmonics at the low frequency of interest of BOLD effects. Even shorter TR values would be required if high-order harmonics were considered. At the typical TRs used for whole brain imaging (i.e. 2 or 3 s), cardiac and physiological fluctuations mix with the BOLD fluctuations of interest. Therefore, they cannot be removed via simple band-pass or notch filtering unless brain coverage is reduced to shorten TR (Lowe et al., 1998) or fast

imaging protocols are adopted, such as MR-inverse imaging (Hennig et al., 2007; Kiviniemi et al., 2016; Lin et al., 2012) and simultaneous multislice (SMS) EPI (Feinberg et al., 2010; Moeller et al., 2010) (but see Scheel et al. (2014) for the need of physiological noise regression in SMS EPI data).

Importantly, respiration, cardiac rate and arterial pressure are non-stationary processes, with mutual interactions governed dynamically by the two main branches of the autonomic nervous system, the sympathetic nervous system and the parasympathetic nervous system (Berntson et al., 1997), as well as the renin-angiotensin system (Akselrod et al., 1981). Several works have demonstrated significant correlation between the BOLD signal and time series modeling low frequency changes in respiratory rate (Birn et al., 2006; Wise et al., 2004) and cardiac rate (Shmueli et al., 2007). Low frequency fluctuations in cardiac rate (CR) occur at a frequency of about 0.04 Hz (Shmueli et al., 2007). Variations in respiratory rate affect the fMRI signal by changing the oxygenation level and the arterial level of CO_2, a potent cerebral vasodilator (Birn et al., 2006). Although this effect can be clearly observed in response to a hypercapnic or breath-holding challenge (Bright et al., 2009; Bulte et al., 2012; Kastrup et al., 1998, 1999a, 1999b; Li et al., 1999), it also naturally occurs during normal breathing where subtle variations in the depth and rate of breathing cause small fluctuations in end-tidal pressure of CO_2 ($P_{ET}CO2$) at a frequency of about 0.03 Hz (Birn et al., 2006; Wise et al., 2004).

Fluctuations in the cardiac rate as typically considered in denoising the fMRI signal should not be confounded with the concept of heart rate variability (HRV), a physiological phenomenon that is widely used as a marker of autonomic nervous activity (Berntson et al., 1997; Task Force, 1996). The normal rhythm of the heart is controlled by membrane processes of the cardiac sinoatrial node, which receives inputs from both the sympathetic and parasympathetic nervous systems. It exhibits two main frequency components. The high frequency component of HRV (0.15–0.4 Hz) is associated with the respiratory sinus arrhythmia, a naturally occurring variation in heart rate during the breathing cycle that is driven by vagal activity, i.e. related to parasympathetic activity. For instance, this process controls heart rate increases during inspiration and decreases during expiration. The origin of the low frequency component (0.04–0.15 Hz) of HRV is less understood, but is thought to be associated with cyclic changes or Mayer waves of blood pressure at frequencies slower than respiratory frequency, and is believed to reflect fluctuations of sympathetic as well as parasympathetic activity (Berntson et al., 1997). The low and high frequency components of HRV can be extracted by performing a time-frequency analysis using wavelets (Chang et al., 2013) or the Smoothed Pseudo Wigner Ville Distribution (Gil et al., 2010). Heart rate variability is correlated to regional BOLD signal variations induced by multiple experimental paradigms (Iacovella and Hasson, 2011), such as emotion (Critchley et al., 2005), pain (Sclocco et al., 2016), and cognitive tasks (Basile et al., 2013), as well as when assessing the function of the autonomic nervous system during task performance (Napadow et al., 2008) or at rest (Chang et al., 2013). In that respect, it is relevant to consider that some neuropsychiatric diseases, e.g. depression, are associated with low heart rate variability (Kemp et al., 2010). Additional potential physiological confounds of the fMRI signal are the low frequency fluctuations due to vasomotion occurring at approximately 0.1 Hz, which are related to the slow cycling of arterial vessel diameters to control vascular tone (Aalkjær et

al., 2011) as well as cerebral autoregulation mechanisms that maintain steady cerebral blood flow despite fluctuations in blood pressure (see Murphy et al., 2013 for a review).

In summary, apart from the main components related to the respiratory and cardiac cycles, the BOLD signal also inevitably comprise physiological fluctuations related to very low and low frequency changes of respiration rate, cardiac rate and vasomotion that interact with each other and manifest themselves through changes in arterial CO_2, blood pressure and vascular tone.

4.2. Denoising physiological noise based on external recordings

Nowadays, most MR scanners have equipment for physiological monitoring of respiration and cardiac pulse. A trace of respiration is typically measured by means of a pneumatic belt placed around the subject's abdomen, whereas the cardiac pulse is typically measured by means of a pulse oximeter or photoplethysmograph (PPG) placed in the pad of the finger or toe. Pulse oximetry provides a direct assessment of changes in global blood oxygenation by measuring the absorption of infrared light transmitted through blood infused tissue (Nilsson, 2013). Alternatively, lead systems might also be available to capture the electrocardiogram (ECG) or vectorcardiogram (VCG). Nevertheless, the use of pulse oximeters is usually preferred to ECG systems for cardiac recordings since the latter may not be easy to place in certain populations (e.g. infants, elderly) and the ECG signal is corrupted by MR-gradient artefacts. Remarkably, if respiration signals were unavailable or corrupted, they can also be extracted from ECG or VCG signals, known as ECG-derived respiration (Bailón et al., 2006; Labate et al., 2013), or from the PPG (Lázaro et al., 2012; Nilsson, 2013). However, deriving respiratory signals from cardiac or pulse recordings is a strategy that has been scarcely employed for denoising fMRI data (Abreu et al., 2016; Verstynen and Deshpande, 2011; van Houdt et al., 2010).

In the simplest approach, the fundamental frequencies of the cardiac and respiratory fluctuations can be identified from corresponding peaks in the spectrum of the external recordings. Next, notch filters can be defined at the fundamental frequencies, and harmonics if necessary, to remove these signals (Biswal et al., 1996). The drawback of notch filtering is that it will also remove any BOLD fluctuation of interest that could exist at these frequencies. In addition, these fluctuations do not exhibit a constant frequency, showing multiple spectral peaks; thereby a minimum bandwidth of the notch filter or several notch filters must be specified in order to remove all the effects.

As a consequence, multiple modeling approaches have been developed to reduce the primary effects of cardiac and respiratory cycles in a retrospective manner. Among them, RETROICOR (Glover et al., 2000) is probably the most common method. Assuming that cardiac and respiratory fluctuations can be modeled as quasi-periodic processes, RETROICOR models them by means of a low-order Fourier series with time-varying cardiac and respiratory phases, which are fit to the data as nuisance regressors and removed. The cardiac phase is estimated as the difference between the time at which the image was acquired and the previous cardiac peak, relative to the R-peak interval. The respiratory phase is estimated by a histogram-equalized method from the amplitude of the respiratory signal. Since the phases of the cardiac and respiratory cycles are matched with the timing of

each imaging slice, RETROICOR is able to cope well with aliasing in low frequencies as well as non-stationary cardiac and respiratory frequencies (Glover et al., 2000). In general, two harmonics are generally employed in the Fourier expansion of each component. Models including higher orders and interactions between the cardiac and respiratory cycles, for example to describe the effect of respiratory-induced pressure changes on the cardiac rhythm, have been shown beneficial in areas substantially affected by physiological noise such as the brainstem (Brooks et al., 2008; Harvey et al., 2008). However, in general, these complex models are not relevant in the entire cortex (Beall, 2010). Still, similar to other approaches based on nuisance regression, adding more physiological noise regressors does not necessarily lead to improvement in BOLD sensitivity and higher statistical significance due to the loss in degrees of freedoms and possible correlations of the physiological regressors with the BOLD fluctuations generated by the experimental paradigm in task-based fMRI or the intrinsic neuronal fluctuations in the resting state. Hence, the optimal set of regressors will depend on the sequence and parameters of acquisition, as well as the regions of interest (Hutton et al., 2011; Tijssen et al., 2014). To overcome this ambiguity, Beall (2010) goes beyond the RETROICOR model and proposes an adaptive estimation of the cardiac and respiratory impulse response functions (IRFs) only from those voxels where the fitting of the RETROICOR model is statistically different from a fitting obtained with random regressors. This IRF approach proved to be more efficient than RETROICOR in terms of the number of degrees of freedom used for denoising. The idea of estimating the cardiac and respiratory IRFs has also been explored by Deckers et al. (2006), where both IRFs are computed by simple averaging the fMRI time series to the physiological events (e.g. peaks in heartbeat or respiration traces), and these templates are subsequently used in an average artefact subtraction algorithm.

RETROICOR operates in the image space, i.e. it fits and reduces the noise in each voxel time series independently. Therefore, it overcomes the drawbacks of correcting physiological noise by retrospectively fitting a set of Fourier terms defined from the physiological recordings directly in the k-space, a method later referred to as RETROKCOR (Hu et al. 1995; Le and Hu, 1996). In RETROKCOR, denoising in *k*-space entails calculations in the magnitude and phase (or the real and imaginary) *k*-space data for each individual channel in multichannel coils (Nc). The number of calculations is 2 x Nc regressions in total for each *k*-space point, compared with only one regression on the magnitude data that is required in image space, or two regressions if both magnitude and phase data are denoised (Petridou et al., 2009). Furthermore, since inner frequencies of the *k*-space have higher SNR values than outer frequencies, the fitting of the Fourier terms will be more accurate in the inner frequencies than in the outer frequencies. This will introduce spatial blurring after the k-space data is transformed into the image domain, as well as potentially modify the signal in voxels where physiological artefacts might not be prominent and denoising is not necessary (Tijssen et al., 2014). To overcome the limitations of the original RETROKCOR approach, Frank et al. (2001) proposed to reorder the *k*-space data into the order in time in which it was collected, rather than spatial order as usual, in order to effectively reduce the TR to a nominal value of TR divided by the number of slices. With such a fast TR, global physiological fluctuations can be identified with higher accuracy in the *k*-space origin and subsequently removed (Frank et al., 2001). Even using this

approach, denoising in the *k*-space is problematic for reducing localized cardiac-induced and respiratory noise since the signal power of localized effects in image space is spread across low and high k-space frequencies (Glover et al., 2000). Interestingly, despite operations are typically performed on magnitude and phase data, it has been shown that the problems associated with the correction of the higher spatial frequencies in *k*-space in RETROKCOR can be largely mitigated by performing the correction on the real and imaginary part of the data (Tijssen et al., 2014). Of note among the k-space techniques for physiological denoising is the method of k-space nuisance variable regression (NVRk) (Hagberg et al., 2012). In NVRk, a single nuisance variable regressor is defined on the phase evolution of the central k-space point. This regressor mainly captures respiration-induced changes although cardiac pulsation may also contribute. Contrary to RETROKCOR and RETROICOR, NVRk does not require physiological recordings (Hagberg et al., 2012).

RETROICOR proposes to estimate the respiratory phases based on a histogram-based approach considering the entire waveform of the signal (Glover et al., 2000) instead of with a peak detection algorithm that estimates the respiratory phase in a similar manner as for the cardiac phase based on the timings of peak inspiration (Hu et al., 1995; Lund et al., 2006; Verstynen and Deshpande, 2011). This feature of RETROICOR is crucial to effectively remove respiratory-induced signal changes since susceptibility changes and head movement depend on the entire shape of the breathing cycle (Raj et al., 2001; van de Moortele et al., 2002), and not only on the timing of peak inspiration. The respiratory phase needs to increase nonlinearly with time as it changes considerably around the time of inspiration and expiration, and remains constant in between. A peak detection approach can only model a linear increase in the respiratory phase, which might not be sufficient except for short TR acquisitions and if comprehensive modeling of the motion-related effects is performed (Lund et al. 2006). It is important to highlight some physiological monitoring units autoscale the amplitude of the respiration recordings in order to avoid any saturation of the signal. Therefore, it is recommendable to stop the autoscaling function or avoid any saturation effect for correction of respiration effects.

Furthermore, in RETROICOR the coefficients of the Fourier terms are assumed to be constant in time. This model implies that the amplitudes of the fluctuations are also assumed to be constant in time, which is an unrealistic assumption in real data. The DRIFTER algorithm overcomes this limitation (Särkkä et al., 2012), where the Fourier series are represented in terms of differential equations (oscillators) with time-varying frequencies, plus a white noise component to account small changes in the shape of the signal. In DRIFTER, a stochastic state space model is formulated for the quasi-periodic physiological signals, where the frequency trajectories of the physiological signals are estimated by means of an interacting multiple models (IMM) filter algorithm, either from the physiological recordings or directly from the fMRI data if the sampling rate is high enough. The estimation of the stochastic state space model is performed with Kalman filters and Rauch-Tung-Striebel smoother algorithms for each voxel independently, which separates the signal into an activation-related component, cardiac-related and respiration-related components, as well as a white noise component (Särkkä et al., 2012). The dynamic nature of the DRIFTER model makes it track the physiological signals better than the RETROICOR algorithm, particularly when the shapes and amplitudes change over time, without requiring

these changes to be present in the reference traces. In addition, DRIFTER is also robust to the presence of artefacts in the reference signals, such as sudden changes in the DC-level or autoscaling of the waveforms during the recordings (Särkkä et al., 2012). However, a limitation of the DRIFTER algorithm in its current implementation is that the activation-related signal is assumed to be smooth in time, which may fail tracking brief BOLD responses in rapid event-related paradigms. In addition, the activation-related signal also comprises of other components of the signal, such as scanner drifts, motion-related effects or other types of physiological noise, which are not considered in the model and should be removed from the signal in a subsequent step (Särkkä et al., 2012).

Although the vast majority of fMRI studies employ multislice single-shot 2D EPI acquisitions, in recent years multi-shot 3D EPI acquisitions are becoming increasingly popular at 3 T and 7 T to achieve high spatial resolution with larger SNR values than their 2D counterparts (Jorge et al., 2013; Narsude et al., 2016; Poser et al., 2010; van der Zwaag et al., 2012). Unfortunately, multi-shot 3D EPI acquisitions are more sensitive to physiological noise since errors between the k-space segments result in strong temporal fluctuations in image space (Lutti et al., 2013; Tijssen et al., 2011; 2014). Whereas in multislice 2D acquisitions the sampling time of the RETROICOR regressors needs to match the time of acquisition of each slice, i.e. slicewise regressors must be ideally created and fitted to the time series (Jo et al., 2010; Jones et al., 2009), such a straightforward relationship cannot be established in multi-shot 3D acquisitions where the data of each volume depends on volumetric k-space data acquired during several seconds. It has been shown that using volume-specific regressors, where a single physiological phase is assigned to the entire volume, offers similar performance to a more complex model considering segment-specific regressors as long as the timing of the regressor corresponds to the time at which the center of *k*-space is acquired (Lutti et al., 2013; Tijssen et al., 2014). Moreover, in 3D sequences physiological noise correction in the magnitude images with RETROICOR still outperforms correction in *k*-space with RETROKCOR (Tijssen et al., 2014).

The same physiological recordings can also be employed to reduce low-frequency BOLD fluctuations related to varying respiratory and cardiac rates. On the one hand, variations in respiratory rate can be reduced by regressing out the effect of the respiration volume time series (RVT), which aim to represent the amount of air inspired with each breath and thus is assumed to be correlated with fluctuations in arterial CO_2 concentrations. Two main definitions of RVT have been proposed. First, Birn et al. (2006) defined RVT by computing the difference between the maximum and minimum amplitudes of the respiratory trace at the peaks of inspiration and expiration, respectively. This difference is normalized by the respiration period (i.e. the interval between two successive maxima). Alternatively, Chang et al. (2009) defined RVT by computing the standard deviation of the respiratory waveform on a sliding window basis (e.g. window of 3 TRs centered at each TR sampling point). While the RVT in Chang et al. (2009) represents the root-mean-square (RMS) average over a sliding window and does not rely on the accuracy of detecting respiration peaks and valleys, the RVT in Birn et al. (2006) accounts more explicitly for variations in breathing rate by normalizing the depth by the breath-to-breath interval. As expected, in practice both definitions are highly correlated, although models using the RVT in Chang et al. (2009) tend to explain more signal variance. Likewise, a cardiac rate (CR) time series characterizes

variations in cardiac rate by averaging the interval between pairs of adjacent heartbeats on a sliding window basis and resampling to TR resolution (Shmueli et al., 2007; Chang et al., 2009). Once the CR and RVT time series are obtained, the simplest approach to reduce low-frequency cardiac and respiratory fluctuations is to initially compute the correlation of these time series and the fMRI signal at multiple time shifts (both positive and negative) and then regress out the time series corresponding to the latencies with maximum absolute correlation (Birn et al., 2006; Shmueli et al., 2007). For that, the optimal latency could be identified and regressed out for each voxel independently (Birn et al., 2006) or based on the mean correlation curve across voxels in GM, WM or the whole-brain (Shmueli et al., 2007). If the correlation curve exhibited multiple significant latency time points (e.g. maximum and minimum), multiple shifted waveforms could also be included in the regression. Eventually, a model including all shifted time series could be incorporated in the regression to explain the most variance (Shmueli et al., 2007), although this might considerably reduce the degrees of freedom.

Assuming that the relationship between the RVT and CR fluctuations and the BOLD signal follows a linear model, a more established approach to determine the nuisance regressors is to convolve the RVT and CR time series with a respiratory response function (Birn et al., 2008) and cardiac response function (Chang et al., 2009), respectively. Both cardiac and respiratory response functions can be estimated by voxelwise deconvolution of the fMRI signal according to a smooth Finite Impulse Response (FIR) model (Goutte et al., 2000), and then averaging across voxels and subjects to obtain representative response functions (Birn et al., 2008; Chang et al., 2009). To account for possible interactions between RVT and CR, it is more recommendable to deconvolve both RVT and CR simultaneously as opposed to deconvolve each of them individually (e.g. see Birn et al., (2008) for RVT). This combined model is referred to as the RVHRCOR model (Chang et al., 2009). The RVHRCOR model was extended in Golestani et al. (2015) to additionally estimate the $P_{ET}CO_2$ response function by using $P_{ET}CO_2$ measurements, in addition to cardiac and respiratory traces, and enable modeling of $P_{ET}CO_2$-related fluctuations. Respiratory processes might be compensated more effectively by using more direct measurements of CO_2 in the body such as $P_{ET}CO2$, rather than indirectly through RVT (Chang and Glover, 2009b; Golestani et al., 2015).

In practice, using across-subject averages of the respiratory, cardiac and $P_{ET}CO2$ response functions might prevent us from capturing interindividual differences in physiology. Therefore, several authors have proposed to estimate subject-specific response functions that are cross-validated in separate datasets (Cordes et al., 2014; Falahpour et al., 2013; Golestani et al., 2015). For instance, Falahpour et al. (2013) performed the deconvolution of both response functions using the RVHRCOR approach except using the global signal instead of voxels as the input signal since physiological noise can be assumed dominant over thermal noise after averaging across voxels. An optimization algorithm that penalizes the curvature of the weighted sum of the standard cardiac and respiratory response functions plus their derivatives in time is proposed in Cordes et al., (2014). These studies have demonstrated inter-subject and acquisition-dependent (e.g. TR) variability in the response functions with respect to the original response functions determined by averaging across subjects, suggesting that a subject-specific characterization of the response functions might help

reducing low frequency physiological fluctuations at the subject level, being particularly important in clinical applications.

In any case, it is important to highlight that the variance explained by the low-frequency cardiac-related and respiratory-related fluctuations is less spatially localized than the primary effects related to the cardiac and respiratory cycles that are generally modeled with RETROICOR. Instead, the low frequency components are complementary to each other, and cover across widespread areas of the brain, mainly in regions such as the posterior cingulate, angular gyrus and medial frontal, which are commonly included in the default mode network and show negative signal changes during task performance (Birn et al., 2006; 2008; Chang and Glover, 2009a; Shmueli et al., 2007), as well as in the frontal, occipital and insular cortices (Shmueli et al., 2007). This demonstrates that it is worth it to consider a full model including all RETROICOR regressors as well as low frequency components based on RVT and CR since they capture different physiological mechanisms affecting the fMRI signal.

If respiratory recordings with pneumatic belts were not available or corrupted, both respiration and cardiac events can be extracted from the low frequencies (0.2 – 0.5 Hz) and high frequencies (0.6 – 2.0 Hz) of the raw pulse oximetry signal (i.e. without filtering or gain adjustment) using a peak detection algorithm (Nilsson, 2013; Verstynen and Deshpande, 2011). The peaks correspond to individual maxima in local blood oxygenation and are delayed from the time of the mechanical events that trigger them, either related to contractions of the heart muscles or the points of maximum diaphragm expansion. The timing information of these events can then be used to define the phase of the quasi-periodic fluctuations induced by the heart rate and the respiratory rate as it is done in RETROICOR, as well as to characterize variations in the cardiac rate (Shmueli et al., 2007; Chang et al., 2009) or respiratory volume (Birn et al., 2006; 2008). In practice, differences in the sensor placement site and variability in the vascular system across individuals, i.e. differences from the origin of the mechanical event to the recording site and also to brain tissue, make it difficult to determine the shift of the pulse oximetry signal that optimizes the denoising of the physiological confounds. Furthermore, the optimal time shift is likely to vary across brain regions. Therefore, in some cases a finite impulse response regression model including multiple shifted signals at different lags may be more appropriate than selecting a constant phase shift (van Houdt et al., 2010), although the corresponding loss in the number of degrees of freedom and potential risk of overfitting must be considered. Using data from a blocked eye movement task, Verstynen and Deshpande (2011) demonstrated that the maps of the physiological confounds explained by models using the filtered pulse oximetry signals exhibited significant overlap with those obtained using the signals from the ECG and pneumatic belt. Maps from the pulse oximetry models were more similar to the maps obtained by RETROICOR than those by RVT and CR. This fact could potentially arise from the fact that a phase lag might not be as appropriate as convolving the physiological time series with respiratory and cardiac response functions (Birn et al., 2008; Chang et al., 2009). Variations in the pulse height of the raw pulse oximetry signal can also directly account for physiological noise without the need of additional convolutional operators, mainly capturing respiratory mechanisms that are complementary to changes in respiratory volume (Birn et al., 2006) rather than mechanisms related to respiratory cycles as modeled in RETROICOR (van Houdt et al., 2010).

As a final note, changes in blood pressure can also be monitored with MR-compatible continuous blood pressure devices, for instance by estimating arterial stiffness through pulse wave velocity measurements (Murphy et al. 2011) or using the Caretaker device (BIOPAC) (Whittaker et al., 2016). These time courses can then be regressed out from the fMRI signal with the purpose of minimizing intrinsic fluctuations associated with cerebral autoregulation and changes in blood pressure (Murphy et al., 2013). Blood pressure signals can be also extracted via the peak amplitudes of the pulse oximetry signal (Cannesson et al., 2005), although to our knowledge this strategy has been used occasionally for fMRI data analysis (Power et al., 2016).

4.3. Data-driven denoising methods of physiological noise

As an alternative to external physiological monitoring, data driven techniques for physiological noise correction can be useful in cases when physiological monitoring is not available, the recordings are corrupted, or it was not possible to obtain them in non-compliant/uncomfortable subjects. In addition, data driven methods have the theoretical benefit of directly identifying physiological confounds without the need of a pre-established signal model.

If the TR is short enough, the primary frequencies of the cardiac and respiratory signals will not alias with the BOLD response. Hence, these components can be easily removed with a band-pass or notch filter (Biswal et al., 1995; Lowe et al., 1998). This assumption is also the basis of the IMage-based Physiological Artifacts estimation and Correction Technique (IMPACT) (Chuang and Chen, 2001). Unfortunately, a notch filter will also remove any possible neural-related BOLD fluctuation existing at the same frequencies. For instance, respiratory fluctuations in a subject with a slow respiration cycle (e.g. below 0.2 Hz) will probably alias with the highest frequencies of the BOLD response in a fast randomized event-related design. Similarly, frequency filtering cannot be applied to remove low-frequency physiological fluctuations, related to variations in cardiac rate or respiratory volume, arterial CO_2 or blood pressure variations, since these fluctuations coexist at the same frequencies of neural-related BOLD signal changes.

Rather than using a notch filter, if a digital filter is to be employed for denoising task-based fMRI data it is preferable to consider both the power spectrum of the task-related activity and the physiological fluctuations. For instance, Buonocore and Maddock (1997) developed an adaptive Wiener filtering strategy where the power spectrum of physiological noise was estimated from voxels in the ventricles, the power spectrum of random noise from white matter voxels, and the power spectrum of task-related activity from the fMRI signal itself. A limitation of this approach is that the spectral characteristics of physiological fluctuations are assumed to be identical across the entire brain.

Also, note that the TR of the acquisition could be adapted in a subject-by-subject basis if the heart and respiratory rates were relatively constant in time at the individual level so that the aliasing of physiological noise with effects of interest is prevented or, at least, reduced such that frequency filtering may become a valid option (Cordes et al., 2014). Although this strategy might be a valuable solution in clinical studies with single individuals, particularly at rest where rates are relatively stable, it is unclear whether TR-adaptive protocols could

be adequate in studies where the cardiac and respiratory rates is modulated by the task (Birn et al., 2009; Hillenbrand et al., 2016; Iacovella and Hasson, 2011). Also, in group studies this approach would introduce variability in the number of volumes and the temporal characteristics of the BOLD and noise components across subjects.

Therefore, when neuronal-related BOLD fluctuations are inevitably aliased with physiological noise fluctuations, alternative data-driven methods must be used for reducing physiological noise without the need of physiological recordings. To begin with, one should notice that the majority of the decomposition methods described in sections "*Denosising methods based on principal component analysis (PCA)*" and "Denoising methods based on independent component analysis (ICA)" can determine regressors or components related to physiological noise such that they are subsequently removed. Although some approaches are specifically developed toward the removal of motion-related effects, physiological-related components will also be identified due to the inherent links that exist between motion, respiration and cardiac pulsatility. Similarly, tissue-based nuisance regressors obtained from CSF of the lateral ventricles, WM or extracerebral soft tissues can also account for cardiac and respiratory-related fluctuations to some extent if these fluctuations are dominant components of the signal in these regions (e.g. Anderson et al., 2011; Jo et al., 2010). The principal components defined in the CompCor algorithms (Behzadi et al., 2007) can achieve similar estimation of physiological cardiac and respiratory fluctuations to RETROICOR.

Several ICA-based methods have been specifically developed for physiological noise correction. The CORSICA algorithm employs spatial ICA to identify components related to physiological noise by evaluating the correlation between the IC time courses and signals from regions that are known to exhibit major physiological fluctuations, such as the lateral ventricles for respiratory-related fluctuations and the basilar arteries for cardiac fluctuations (Perlbarg et al., 2007). On the contrary, temporal ICA is applied in the PESTICA algorithm (Beall and Lowe, 2007) since its main goal is to estimate and disentangle the time courses related to cardiac and respiratory fluctuations directly from the data, which must be similar to parallel recordings of heartbeat and respiration. In PESTICA two options are available for the selection of the physiological-related temporal ICs. The first option selects those components whose spatial maps exhibit the maximum correlation with prior spatial maps of physiological components. The second option is based on the correlation of the IC time courses with physiological recordings if these were also available (Beall and Lowe, 2007). These data-driven physiological traces can then be used for retrospective noise correction with RETROICOR (Glover et al., 2000) or RETROKCOR (Hu et al., 1995). The estimated traces might be more representative of cerebral physiological signal since, theoretically, they do not have the phase shift associated with the distance between the site of the recording, e.g. the finger, and the brain (Beall and Lowe, 2007). Also, the time traces estimated by PESTICA can be used to compute cardiac and respiratory impulse response functions to improve the fitting obtained by RETROICOR (Beall, 2010). With a similar goal to PESTICA, a multiclass support vector machine classifier can also be used to assign each fMRI volume to a certain bin within the physiological phase cycle and thereby predict the cardiac and respiratory phase time series from the fMRI data every TR. These physiological phase time series can then be incorporated into RETROICOR (Ash et al., 2013).

Finally, beyond PCA- and ICA-based methods, Churchill et al. (2012c, 2013) developed a multivariate framework for physiological noise correction based on an adaptation of canonical correlation analysis (CCA), termed Physiological Correction using Canonical Autocorrelation Analysis (PHYCAA). The initial version of the PHYCAA algorithm identifies high frequency autocorrelated physiological noise sources with reproducible spatial structure in task-based fMRI (Churchill et al., 2012c). The selection of the physiological noise components was constrained to those with more than 50% of the power spectrum above 0.1 Hz. The PHYCAA+ algorithm (Churchill et al., 2013) uses spatial maps of probable non-neuronal tissue, based on both the frequency content of the component and the spatial overlap with segmented CSF probabilistic maps. The addition of these features improved the selection of the physiological noise components. Importantly, the PHYCAA algorithms estimate physiological noise components that are orthogonal to the estimated BOLD response to the task. For that, the algorithms use a cross-validation strategy, thus requiring a least two datasets, to determine the physiological regressors that optimize the reproducibility and prediction of task-related activations. As such, the PHYCAA(+) methods minimize the possibility of removing BOLD signal that might be mixed with physiological noise, for example in cases where changes in heart or respiration rate may be modulated by task performance (Iacovella and Hasson, 2011).

5. Denoising methods based on multi-echo fMRI

All denoising methods described in the previous sections assume that the fMRI signal is sampled at a single echo time (TE), which is typically close to the average grey matter T2* of targeted regions. However, it has been long recognized that multi-echo EPI acquisitions, where the fMRI signal is sampled at multiple TEs, improve the sensitivity to the BOLD response relative to standard single-echo acquisitions. To optimize BOLD sensitivity, the signals of the multiple echoes must be linearly combined with weights depending on the TE and the voxel T2* or tSNR values (Bhavsar et al., 2014; Buur et al., 2008; Chiew and Graham, 2011; Gowland and Bowtell, 2007; Poser et al., 2006; Poser and Norris, 2009; Posse, 2012; Posse et al., 1999; Schmiedeskamp et al., 2010; Speck and Hennig, 1998). As a result, the combined fMRI signal has a better contrast-to-noise ratio mainly due to the reduction in thermal noise, which can be exploited for increasing the sensitivity and specificity for task-based and resting state experiments at different field strengths. Multi-echo fMRI offers clear advantages for imaging brain regions such as the orbitofrontal cortex and inferior temporal lobes, which are prone to susceptibility distortions and signal dropouts (Halai et al., 2014; 2015).

Crucially, the multi-echo signals differ from each other in terms of T2*-weighting and thermal noise, but not in terms of T1 weighting. Consequently, apart from enhancing BOLD sensitivity, the properties of multi-echo fMRI can be exploited in different ways for denoising purposes. If two echoes are collected (i.e. dual-echo), signals can be recorded at a short TE which is assumed to have minimal T2*-weighting and mainly sensitive to fluctuations in the net magnetization S_0. The short TE signal can then be regressed out from time series acquired at a longer TE that is optimized for BOLD sensitivity (Bright and Murphy, 2013; Buur et al., 2008). An initial proof of concept of this strategy was proposed in Talagala et al. (1999), where short TE and optimal TE signals were alternatively

collected. Likewise, Ing and Schwarzbauer (2012) proposed to compute the division of the two echo signals. Importantly, any of these approaches could be used alongside weighted echo combination if more than two echoes were collected. As a matter of fact, the S_0 signal could also be estimated by collecting a large number of echoes (Speck and Hennig, 1998) and then removed from the echo signals.

The attractiveness of short-TE methods comes from the fact that it is effectively “free” to acquire, with a negligible increase in temporal resolution, and helps to effectively reduce motion-related fluctuations, signal drifts, inflow effects and, to a lesser extent, physiological noise (Bright and Murphy, 2013). Furthermore, being a data-driven approach, it is able to fully capture the effects of within-volume motion effects and spin history artefacts. In fact, its efficacy correlates with the extent of motion, i.e. the larger the motion, the better it works (Bright and Murphy, 2013; Buur et al., 2008). Short-TE regression approaches have demonstrated improvements of functional connectivity estimates in resting state data (Bright and Murphy, 2013; Ing and Schwarzbauer, 2012). Nevertheless, it is interesting that regressing out the short-TE signal has also resulted in a reduction in the magnitude and extent of the response to a task when motion is not a dominant effect. It is still unclear whether this reduction arises from residual BOLD contamination or task-correlated blood volume effects in the short TE signal (Bright and Murphy, 2013; Buur et al., 2008). Regardless of the cause, this observation highlights the need of selecting the short TE as close to zero as possible to minimize any BOLD contamination in the signal, which would be subsequently removed from the second TE or combined signal. If BOLD contamination is expected, it is advisable that the short-TE signal is included as nuisance regressor in the model along with regressors of interest, or to orthogonalize the short-TE regressor with respect to the regressors of interest prior to further analyses. In this context, the division method described by Ing and Schwarzbauer (2012) is robust against BOLD contamination in the short TE signal. However, this division method requires the second TE to be longer than that used in regression-based approaches in order to optimize contrast-to-noise ratio of the denoised signal, and this decreases the temporal resolution of the acquisition (Ing and Schwarzbauer, 2012).

On the other hand, Kundu et al. (2012) proposed a multi-echo denoising strategy based on independent component analysis (ME-ICA). This method exploits the fact that BOLD components must exhibit a linear dependence with TE, whereas non-BOLD components must exhibit no dependence with TE. The ME-ICA algorithm initially performs the spatial ICA decomposition of the optimally-combined multi-echo signal (Poser et al., 2006: Posse et al., 1999). Next, two summary statistics, kappa and rho respectively representing the amount of BOLD signal change (ΔR_2^*) or spin-density (or inflow) signal change (ΔS_0), are computed voxel-wise for each spatial component, and then averaged across the brain. A combination of low kappa and high rho indicates the component has a low dependence on TE and a high likelihood of being a non-BOLD component. In contrast, a combination of high kappa and low rho indicates the component has a high dependence on TE and a high likelihood of being a BOLD component. The components are then classified based on the values of kappa and rho, as well as other metrics such as explained variance. Similar to other ICA-based methods, the final step of ME-ICA is to regress out from the data those ICs that are classified as noise (Kundu et al., 2012; 2013; Olafsson et al.,

2015). ME-ICA has demonstrated an excellent efficiency in distinguishing artefactual and motion-related components that are only coupled to changes in S_0 (ΔS_0). For instance, ME-ICA was able to identify the high-frequency spatial artifact due to the mixing of slices that were simultaneously excited in multi-echo simultaneous multislice acquisition (Olafsson et al., 2015). A less clear distinction occurs for those components that are simultaneously coupled to changes in S0 (ΔS_0) and R2* (ΔR_2*) (i.e. showing a high rho and high kappa value), for instance certain cardiac and respiratory-related fluctuations showing a dependence on TE (Krüger and Glover, 2001). For these components, the decision can be complemented with other informative metrics, such as the correlation between the IC time course and physiological regressors (e.g. RVT, CR or RETROICOR). The efficacy of ME-ICA in denoising has been demonstrated in a variety of low-level (e.g. visual and motor) and high-level cognitive tasks (e.g. visual, motor, listening music, mentalizing, reading) across blocked or event-related designs (Evans et al., 2015; Gonzalez-Castillo et al., 2016; Lombardo et al., 2016).

Multi-echo acquisitions have also received considerable attention for denoising fMRI signals with a non-constant TR, for example when the start of each volume acquisition is triggered by the peak of the cardiac pulse (cardiac gating) or is coupled to the subject's response. A cardiac gated acquisition is typically employed to freeze pulsation-brain movement in those fMRI studies interested in studying regions largely affected by cardiac pulsation, such as the brainstem, basal ganglia, thalamus, hippocampus and amygdala (Beissner et al., 2010; Guimaraes et al., 1998; Napadow et al., 2008). However, since the TR between successive acquisitions is not constant, cardiac gating introduces a strong T1-related fluctuation in the fMRI signal, which must be corrected to obtain useful results. A similar situation would occur if volume acquisition was triggered by the subject's response. In case of a standard single echo acquisition, the T1-effect of non-constant TR data can be compensated by estimating the signal that each voxel would have had if the TR had been constant based on online estimates of T1 and the average TR of the acquisition (Guimaraes et al., 1998). This compensation approach assumes a constant flip angle of 90° across the brain, which may not be appropriate owing to spatial inhomogeneity of B_1 or if a lower flip angle, e.g. the Ernst angle, is used. To overcome this limitation, Shin et al. (2013) proposed to estimate both the effective T1 and the flip angle simultaneously with Kalman filtering.

Beyond single-echo fMRI sequences, Zhang et al. (2006) and Beissner et al. (2010) demonstrated that fitting a T2* signal based on a double-echo sequence and performing the analysis in that signal outperforms the T1-correction outlined by Guimaraes et al. (1998) at the cost of acquiring a slightly reduced number of slices (but see Gonzalez-Castillo et al. (2016) for opposite results). The fitting of T2* was shown to be superior to dividing the two echoes, probably due to BOLD contamination in the first echo, which for cardiac gating is not typically set as close to zero as for the short-TE denoising approaches described earlier (Bright and Murphy, 2013; Buur et al., 2008; Ing and Schwarzbauer, 2012). Furthermore, the superior performance of the T2*-fitting approach with respect to the T1-correction proposed by Guimaraes et al. (1998) can be explained because, in theory, the T2* signal has also a reduction of motion-related effects and slow drifts apparent in S_0. On the other hand, Gonzalez-Castillo et al. (2016) showed that ME-ICA reliably captures the T1-effect as the main non-BOLD component in cardiac-gated fMRI, yielding larger activation magnitude

and extent than the T1-correction and double-echo T2*-fitting methods. Importantly, both ME-ICA and T2*-fitting methods do not require accurate T1 maps. These results show the potential of ME-ICA to identify and remove other T1-related artefacts, such as inflow effects in constant TR acquisitions, which are difficult to model and account for (Gonzalez-Castillo et al., 2016).

6. Phase-based denoising methods

The use of magnitude-only images is the standard way in BOLD fMRI. However, the phase signal contains biologically relevant information about the vasculature contained within voxels that exhibits susceptibility-related signal changes in response to neuronal activity (Hoogenraad et al., 2001). Hence, considering both magnitude and phase changes helps to enhance the mapping of the BOLD response in terms of sensitivity and spatial specificity in complex-based fMRI analysis (Arja et al., 2010; Calhoun et al., 2002; Kociuba and Rowe, 2016; Lee et al., 2009; Rowe and Logan, 2004; 2005; Tomasi and Caparelli, 2007; Yu et al., 2015), and enables functional quantitative susceptibility mapping (Balla et al., 2014; Bianciardi et al., 2014; Chen and Calhoun, 2016; Özbay et al., 2016).

Unfortunately, a shortcoming associated with the phase signal is its high sensitivity to large-scale artefacts (e.g. bulk motion, respiration-induced B_0 shifts, scanner drifts, artefacts driven by the mechanical vibrations associated with helium pump or the flow of the gradient chilling water), as well as to more localized confounds (e.g. cardiac pulsatility and blood flow from large vessels) (Hagberg et al., 2008; 2012; Menon, 2002; Petridou et al., 2009). These adverse effects are generally more manifest in the phase signal than in the magnitude signal and scale with magnetic field strength (Hagberg et al., 2008; 2012). Therefore, several methods can help the cleaning of the phase signal. As a first step, phase wraps can be efficiently removed by phase unwrapping methods to improve phase stability (Cusack and Papadakis, 2002; Hagberg et al., 2008; Jenkinson, 2003; Tomasi and Caparelli, 2007). More specifically, navigator echoes and dynamic field mapping techniques can compensate scan-to-scan B_0-shifts induced by respiration and slow head movements that generate low spatial frequency phase artifacts (Dymerska et al., 2016; Hahn et al., 2009; 2012; Hahn and Rowe, 2012; Hu and Kim, 1994; Pfeuffer et al., 2002; Roopchansingh et al., 2003). Filtering of the phase signal in the 2D time-frequency domain, for instance based on the Stockwell Transform (Goodyear et al., 2004), can be used to eliminate sporadic high frequency phase variations that remain after correction with navigator echoes or dynamic field mapping. These high frequency phase artefacts are typically originated by movements outside of the imaging field of view (e.g. jaw movements in overt speech, arm or hand movements in reaching, coughs, changes in breathing) and can be clearly detected since they result in brief ghosting artefacts in the fMRI images. In addition, unwanted phase variations related to physiological fluctuations can be removed, for example with RETROICOR (Petridou et al., 2009, Hahn and Rowe, 2012). Alternatively, k-space physiological correction methods could also be employed, such as RETROKCOR when external physiological recordings are available (Hu et al. 1995; Le and Hu, 1996; Tijssen et al., 2014) or, in their absence, the k-space nuisance variable regression (NVRk) (Hagberg et al., 2012). Regression of motion parameters has also been suggested (Hahn and Rowe, 2012). Finally, spatial high-pass filtering in the k-space has also proven as a useful alternative to most of the previous

methods since phase artefacts are mainly characterized by low spatial frequencies (Hagberg et al., 2012).

Another application of the phase signal for denoising is to remove the effect of large vessels in gradient echo fMRI. Large vessels can be several millimeters away from the primary site of neural activity and thus confound spatial localization. A key observation for removal of the BOLD contamination from large vessels is the fact that local changes in the phase of the signal are different depending on whether the voxel is within or close to the microvascular system (< 25 μm radius), where vessels are presumably well localized to the site of neuronal activity and are, to a large extent, randomly oriented, or the macrovascular system (> 25 μm radius). The phase of the signal changes as the oxygenation-dependent phase difference between the intra- and extravascular compartments around vessels changes. Among other factors, this change depends on the orientation of the vessels (as a population) within the voxel with respect to the static magnetic field B_0. Therefore, changes in the phase in response to neuronal activity can only be observed if vessels are not randomly oriented (see Menon, 2002, and references therein); otherwise, phase signal changes would smear across vessels. In other words, both large magnitude and phase signal changes can be observed in voxels within or close to large vessels, whereas large magnitude changes but small phase changes can be observed in voxels with randomly oriented vessels. Based on this observation, Menon (2002) proposed a phase-regression strategy where a linear fit between the phase and magnitude time series is used to estimate and remove BOLD signal contributions from large vessels. The efficacy of this method can be further enhanced if a Savitzky-Golay filter is used to smooth phase time series with low signal-to-noise ratio, for instance due to the larger physiological noise at high MR fields (Barry and Gore, 2014). The suppression of large vessels can also be achieved by deploying a full complex fMRI data analysis model (Nencka and Rowe, 2007). Regardless of the strategy, an advantage of these phase regression methods for denoising the effect of large vessels is that they operate on individual voxels in image space and use the phase signal in each voxel. In other words, the removal of the venous effect critically depends on the fact that each voxel should consider its own phase signal for denoising. For example, Curtis et al. (2014) applied it to visualize major vessels in individual subjects, and then remove their effect at the local scale in resting state data. For comparison, Jo et al., (2010) showed that regressing out the average magnitude signal of the draining vessels across the brain, computed based on segmentation of a high-resolution anatomical volume, resulted in a similar effect to regressing out the average GM signal, which should be avoided in order not to remove neuronal-related BOLD components.

Importantly, although the method of phase regression was specifically developed for the removal of BOLD contamination from large vessels, in principle it cannot discriminate between these effects and other mechanisms causing correlated phase and magnitude changes within a voxel, such as off resonance effects driven by respiration, small head motion, or movements outside the field of view (Barry et al., 2010; Menon et al., 2002; Curtis et al., 2014). In fact, an evidence of this observation is that the phase regression method in Menon (2002) is conceptually equivalent to the phase-based approach described in Cheng and Li (2010) for removing respiratory noise. Therefore, based on the intrinsic ability of the phase regression algorithm to capture different types of artefacts, Curtis

and Menon (2014) have recently combined it with the PCA-based CompCor framework (Behzadi et al., 2007). In the HighCor approach (Curtis and Menon, 2014), magnitude nuisance regressors are defined as the principal components of the voxels with the largest phase-amplitude correlations (e.g. the top 2% of voxels). The rationale of HighCor is that selecting voxels based on the temporal standard deviation (tSTD-CompCor) (Behzadi et al., 2007) might not be sufficient to capture subtle physiological confounds with low peak-to-peak fluctuations, such as artefacts related to the helium pump. Since these artefacts are more clearly seen in the phase time series than in the magnitude time series (Hagberg et al., 2012), they can be compensated if a phase-regression approach is used for voxel selection in CompCor. Despite the potential advantage, both HighCor and CompCor achieved a similar increase in temporal SNR, although both methods seem to be complementary and explain different noise components present in the data because their combination helps to further increase the temporal SNR of the signal (Curtis and Menon, 2014).

In practice, the phase regression algorithm (Menon et al., 2002) should be carried out immediately after data undergoes a correction of low frequency B_0-shifts by navigator echoes or dynamic field mapping, and prior to subsequent preprocessing step typically done in magnitude data. This recommendation for the order in preprocessing is probably applicable to any denoising method involving both magnitude and phase data because image reconstruction provides phase and magnitude data. For instance, the phase regression algorithm should precede the Stockwell Transform (Goodyear et al., 2004) and RETROICOR (Glover et al., 2000) if these are also employed for removal of high-frequency phase artefacts and physiological noise respectively (Barry et al., 2012).

7. Global signal regression

Global signal regression (GSR) removes the average fMRI signal across all the voxels in the brain. The assumption is that any process that is captured globally across the brain cannot be linked to neuronal activity. In other words, the global signal mainly represents all the processes that confound the BOLD fMRI signals, including all instrumental, motion-related and physiological fluctuations, mainly associated with respiratory effects (Power et al., 2016), that occur globally in the background; thereby it must be a confound signal and may be appropriate to remove it. The use of GSR departs from the debate about global or local normalization in PET studies (see Aguirre et al., 1998 and references therein). Then, it naturally moved to task-based fMRI with the denomination of proportional scaling, which forces each volume of a 4D dataset to have the same mean, or using the global signal as a covariate (Aguirre et al., 1998; Desjardins et al., 2001; Gavrilescu et al., 2002; Junghöfer et al., 2005; Macey et al., 2004). GSR was also widely used in the early resting state fMRI studies since it helped to reveal a more consistent and focal pattern of functional connectivity between brain regions, improving the correspondence between resting state correlations, functional neurophysiology and anatomy (Fox et al., 2005, 2009; Greicius et al., 2003).

However, the use of GSR has always been debated since the global signal also includes neuronal-related BOLD fluctuations, particularly if these are strong and widespread across the brain. If the global signal was removed, these neuronal-related fluctuations could also

be removed. GSR introduces a negative bias in the estimated BOLD response, decreasing positive BOLD responses and artificially creating negative ones or “deactivations” (Aguirre et al., 1998; Desjardins et al., 2001; Gavrilescu et al., 2002; Junghöfer et al., 2005; Macey et al., 2004). Similarly, the overall effect of GSR in measures of correlation is to force the average correlation across the brain to be zero (Murphy et al., 2009). GSR may artificially introduce anti-correlations between brain regions, which would otherwise exhibit no significant correlations (Murphy et al., 2009; Weissenbacher et al., 2009). For instance, Murphy and colleagues (2009) demonstrated that the classical result in Fox et al. (2005), which showed that fluctuations in the default mode network are anti-correlated with a task-positive network, disappear if GSR is not performed. But not only does GSR bias correlations downward, it also alters them in an unpredictable way (Saad et al., 2012; 2013). For example, in an area of the brain with a strong GS component due to motion but not BOLD, the result of projecting out the GS would likely introduce an artefactual BOLD component of the opposite sign as the motion component. Similarly, in an area with a strong BOLD component of the GS, projection might introduce a motion component of the opposite sign, while inappropriately removing part of the desired BOLD signal. Such projections can lead to unpredictable distortions of a correlation matrix. As such, GSR biases correlations differently depending on the underlying true correlation structure between regions. Its usage can fundamentally alter short- and long-range interregional correlations within a group, hence potentially introducing spurious group differences in regions that show no true functional connectivity differences (Gotts et al., 2013; Saad et al., 2012). In a scenario where differences between the global signals of individuals is expected, using the average of brain-wide correlations as a measure of global correlation (GCOR) in the group level analysis might be a preferable solution (Saad et al., 2013).

Despite these drawbacks, discerning whether GSR is a beneficial or detrimental step in the preprocessing of real data is a complex question. Consensus has recently been reached that its appropriateness and usefulness depend on the dataset and the scientific question at hand (Murphy and Fox, 2016), and recent work analyzing large datasets has demonstrated that the global signal frequently arises from motion-related and physiological, mainly respiratory, effects, exhibiting a spatially varying correlation across the brain tissues (Power et al., 2016). In that sense, electrophysiological studies are able to offer important alternative contributions regarding GSR. Schölvinck et al. (2010) showed that the high gamma-band (40–80 Hz) band-limited power (BLP) signal from local field potentials (LFP) recorded from a single cortical site in monkeys at rest showed positive correlations with the BOLD signal across most of the cortex. This result demonstrates that the global signal is tightly coupled to underlying neural activity. Furthermore, the amplitude of the global signal also correlates with measures of EEG vigilance and is modulated by caffeine (Wong et al., 2012; 2013Wong et al., 2016a, 2016b). Keller et al. (2013) used electrocorticography (ECoG) recordings in patients with refractory epilepsy and demonstrated that although applying GSR to BOLD signals introduced some anti-correlations that were not apparent in the ECoG data, it generally enhances the correspondence between neuronal activity measured by gamma-band BLP (50–150 Hz) and hemodynamic BOLD activity, confirming the observations in Fox et al. (2009).

All in all, sufficient theoretical and empirical evidence, including contradictory results, has shown that the results of task-related activity or functional connectivity after GSR, or obtained from the global signal, should be interpreted very carefully. In fact, the claim that GSR is crucial to uncover true anti-correlated networks is likely inaccurate. Network anti-correlations in resting–state can still be revealed using more reasoned denoising approaches, such as regressing out the principal components of WM and CSF voxels using CompCor (Chai et al., 2012), physiological noise correction (Chang and Glover, 2009a) or using alternative methods for removing of global signal confounds, for instance the median angle shift method (He and Liu, 2012) or the APPLECOR and PEARCOR methods (Marx et al., 2013). Similarly, although some studies have noted that GSR is very effective at removing motion-related effects (Power et al., 2014; Satterthwaite et al., 2013; Yan et al., 2013a, 2013b), multiple works have demonstrated that the same level of efficacy can be achieved by using other denoising strategies and that, sometimes, the use of GSR might even be detrimental (Chai et al., 2012; Gotts et al., 2013; Jo et al., 2013; Muschelli et al., 2014; Patriat et al., 2015; Patel et al., 2014). Therefore, despite its simplicity, the use of GSR should be firmly justified in both task-based and resting state fMRI studies (e.g. GSR could be an effective and fast denoising option for real-time fMRI). If relevant, results should be shown with and without GSR. Instead, it might be advisable to employ other available denoising procedures, as reviewed earlier, that prevent us from assuming that the global signal does not capture any neuronal activity.

8. Searching for the optimal preprocessing pipeline for denoising

The performance of denoising techniques considerably depends on the preprocessing steps and their relative order in the preprocessing pipeline (Carp, 2012a; 2012b; Churchill et al., 2012a; 2012b; 2015; Hallquist et al., 2013; Jo et al., 2013; Jones et al., 2008; Shirer et al., 2015). Assuming that the data remains in the original subject's space, a standard preprocessing pipeline can include any of the following steps: despiking, slice-timing correction, volume registration (a.k.a. motion correction or realignment), geometrical distortion correction, registration to the subject's anatomical image, physiological noise denoising, nuisance regression, temporal filtering, artefact removal, censoring and data interpolation, and spatial smoothing (Strother, 2006). Multiple types of algorithms can be categorized within each preprocessing step, and each step involves selecting a set of parameters. It is therefore clear that the number of unique data preprocessing workflows can be enormous in fMRI data analysis, which may lead to substantial variability in the quality of the preprocessed data and conclusions from fMRI results (Carp, 2012a; Churchill et al., 2015). In practice, it is unfeasible to assess thoroughly all combinations of preprocessing pipelines. To simplify the evaluation, some studies have attempted to investigate the optimal workflow in a rigorous, systematic manner by only including a subset of options and steps (Carp, 2012a; Churchill et al., 2012a; 2012b; 2015; Jones et al., 2008; Shirer et al., 2015). As a matter of fact, establishing a fixed preprocessing pipeline across all individuals in a study might not even be the best approach. Instead, defining individually-optimized pipelines may be more advantageous if examined with caution and carefully evaluated in terms of reproducibility and predictability of the results (Churchill et al., 2012a; 2012b; 2015).

In practice, the elements of the preprocessing pipeline and their relative order need to be decided according to the characteristics of each dataset. Of course, this is a challenging task and automatized adaptive frameworks must be developed, for instance following Carp (2012b), because the optimal pipeline for a given dataset will likely depend on: a) the MR acquisition parameters (type of sequence, voxel size, TR, order of slice acquisition, slice orientation); b) subject-specific traits that modulate the type of noise existing in the data (level of head motion, respiration pattern, heart rate variability, blood pressure); c) the type of experiment, either resting state or task-based fMRI (block, event-related or mixed designs) and its goals, for instance detection versus efficiency (Liu et al., 2001) or brain-behaviour correlations (Churchill et al., 2015).

Despite the limitless diversity in methods, order and parameters, based on our experience, in the following we suggest some preprocessing guidelines to improve the effectiveness of denoising. We also identify optimal approaches that, although are not currently available in any major software package, could potentially outperform current practices and, in our opinion, deserve further investigation. Whereas some of these solutions involve important efforts in the development of methods, others would be easy to implement by adapting existing workflows and analysis scripts. In the following, we assume that magnitude data is only considered for fMRI data analysis due to its widespread adoption, and refer to the reader to section “Phase-based denoising methods” for established recommendations if both magnitude and phase data are considered in the analysis.

The preprocessing pipeline at the subject level could start by despiking the fMRI data to reduce the contribution of large spike signals that may deteriorate the accuracy of volume registration (Jo et al., 2013). Next, a block of several operations, including physiological noise correction, slice-timing correction, volume registration and correction of magnetic field distortions, could be considered candidate steps to perform. The relative order of these operations is controversial since these operations are all interconnected to each other. In practice, one could consider performing slice-timing correction before volume registration. However, it might be reasonable to reverse this order if there is basically no through-plane motion. The slice ordering, either sequential or interleaved, and the slice gap also matter. For instance, when acquiring slices in an interleaved fashion, the time between excitation of adjacent slices is one half TR. Therefore, there is more opportunity for motion to affect the slice timing and cause spin history artefacts. Crucially, serial application of slice timing correction and volume registration is suboptimal. A more sensible solution would be to combine both volume registration and slice-timing correction in one step (Bannister et al., 2004; Bannister et al., 2007; Roche et al., 2011). Apart from the interaction with slice timing correction, head motion also interacts with the correction of susceptibility-induced distortions, which is typically performed based on measured magnetic field maps (Jezzard, 2012). Ideally, the spatial transformations of volume registration and correction for geometric distortions should be merged in one step, either using a single field map (Andersson et al., 2001; Yeo et al., 2008), or based on two acquisitions with reversed phase-encoding directions (Andersson et al., 2003; Bowtell et al., 1994; Chang and Fitzpatrick, 1992; Holland et al., 2010). Furthermore, the interaction of volume registration with other steps becomes more relevant as multichannel receiver coils have become standard in MRI systems. Head motion and respiratory-related movements can cause substantial inaccuracies

in the estimated receiver field maps used for image reconstruction (Faraji-Dana et al., 2016; Hartwig et al., 2011; Sheltraw and Inglis, 2012), particularly with parallel-imaging acceleration techniques (Sheltraw et al., 2012; Polimeni et al., 2016). To the best of our knowledge, a joint method that simultaneously compensates for head motion, slice timing and geometric distortions has not been yet developed.

Incorporating physiological denoising into the preprocessing workflow further complicates the choice of the order. Jones et al. (2008) found that among all correction orders, first performing volume registration, second physiological denoising with RETROICOR, and third slice timing correction resulted in the largest reductions of the temporal standard deviation in simulations as well as in 8 out of 10 subjects. The second best order was to apply RETROICOR prior to volume registration and then slice-timing correction, which was optimal in the other 2 subjects. It was also observed that, once RETROICOR is performed, exchanging the order of slice-timing correction and volume registration had no significant impact in the results. In contrast, Jo et al. (2013) recommended applying RETROICOR prior to slice-timing correction and then volume registration. This controversy originates from the fact that the optimal order for physiological noise correction depends on type of acquisition and the patterns of motion artefacts in the data. For example, in an axial interleaved acquisition with large through-plane motions due to head nodding, common in fMRI experiments, spatial and temporal interpolations associated with volume registration and slice-timing correction will likely mix voxel time series acquired one half-TR apart. In that case, the phase of the cardiac and respiratory cycles at the time of acquisition of these voxels might be substantially different. Consequently, the performance of physiological denoising will be reduced due to temporal inaccuracies of the physiological nuisance regressors. As a general recommendation, the nuisance regressors of RETROICOR must be defined in a slice-by-slice basis and then projected from the time series in each slice (or voxel) independently since the waveforms depend on the acquisition time of each slice relative to the cardiac and respiratory cycles (Jones et al., 2008). Such a high temporal precision becomes critical as the variability in cardiac rate increases. This is also advisable for the low frequency RVT and CR components of RVHRCOR. In fact, Jones et al. (2008) proposed a motion-modified RETROICOR algorithm to integrate the effects of motion correction into physiological denoising. In that approach, the traditional Fourier regressors of the cardiac component are substituted by voxel-specific Fourier regressors that are determined based on the proportion that each slice contributes to a particular voxel at a certain time. The motion-modified RETROICOR model can be easily extended to account for differences in acquisition times across slices (Jones et al., 2008). Even though slice timing correction is often thought to be unnecessary with short TR or introduce inaccuracies in temporal interpolation with long TRs, it does not alter the analysis results in the worst case, and often improve them for event related designs (Kiebel et al., 2007; Sladky et al., 2011). Thereby, we recommend that slice timing correction is performed after denoising of cardiac and respiratory fluctuations based on physiological measurements. Note, however, that in case of task-based fMRI slice-specific (or voxel-specific) design matrices could also be used with a general linear model analysis in order to avoid applying slice timing correction (Worsley et al., 2002). In conclusion, it seems that the optimal approach would be to integrate these initial four steps (i.e. physiological noise correction, volume registration,

geometric distortion correction and slice timing correction) in a unified and voxel-specific framework. Unfortunately, such an approach still needs to be developed and investigated.

The next operation of the preprocessing pipeline typically involves the alignment of the subject's anatomical image, such as a high-resolution T1-weighted volume, to the functional data. Transforming the anatomical image rather than the functional volumes is more recommended for operations or analyses performed in the subject's space in order to avoid interpolating the functional data. The resulting spatial transformation can be applied to the volumes resulting from a tissue-based segmentation or brain parcellation in order to compute tissue-based nuisance regressors or constrain subsequent data analyses within voxels of interest, for instance GM voxels. As noted above, functional data acquired with EPI is prone to geometric distortions that complicate the alignment with the anatomical image if the distortions are not previously corrected. An inversion-recovery (IR)-EPI volume with T1-weighted contrast with the same or higher spatial resolution as the functional data will have the geometric distortions matched to the functional data and can serve as an intermediate reference image to improve anatomical-functional registration or be directly segmented into different tissues (Renvall et al., 2016).

The final steps of the preprocessing comprise spatial smoothing, and the combination of nuisance regression, temporal filtering and censoring. The nuisance regressors might include those ones derived by PCA- or ICA-based methods. The order of these two steps can be exchanged, even if nuisance regressors are defined on anatomical masks (e.g. WM or ventricular CSF) as in the CompCOR or ANATICOR approaches, as long as the tissue-based nuisance regressors are derived before spatial smoothing in order to avoid mixing contributions from different tissue types (Jo et al., 2013). Spatial smoothing reduces uncorrelated noise as well as helps to improve the spatial inter-subject correspondence in group studies. Typically, spatial smoothing is performed with an isotropic volumetric kernel (e.g. a Gaussian kernel with a full-width half maximum larger than the voxel size). In a more elaborated manner, restricting spatial smoothing to voxels within the GM mask (e.g. using the 3dBlurInMask function in AFNI) (Jo et al., 2010) or performing surface-based smoothing (Jo et al., 2007; 2008) reduce the contribution of signals from voxels in draining veins or white matter that have different noise properties. These alternative approaches to isotropic spatial smoothing take full advantage of improvements in the spatial and temporal resolutions achievable with advanced sequences and acquisition protocols. For example, ICA-based denoising approaches benefit from a cortex-based analysis at the single-subject level (Formisano et al., 2004), particularly for high resolution fMRI studies (De Martino et al., 2011).

For resting state fMRI data, it is best to perform temporal filtering (i.e. low-pass, high-pass or band-pass filtering), nuisance regression and censoring simultaneously in a unique regression model to minimize potential errors in data denoising. First, filtering in the frequency domain (e.g. with Butterworth filter) requires continuous data and may introduce spurious fluctuations in the time points surrounding large amplitude spikes that might remain in the data at this point of the preprocessing (Carp, 2013). As a solution, filtering can be implemented by including sine and cosine functions in the regression model. Second, because the same type of frequency filter must be also applied to the nuisance regressors.

Otherwise, if this is not performed in a correct manner, the variance explained by the nuisance regressors in the cutoff frequencies will be reintroduced in the data (Hallquist et al., 2013; Weissenbacher et al., 2009). Third, censoring can be easily handled in a regression model by removing the rows of the regression matrix corresponding to the censored time points.

Finally, one aspect of temporal filtering that may be commonly ignored is its costs in terms of degrees of freedom (DoF), which depends on the filter specification, the duration of the data and the TR. For instance, let us assume we have collected 3 different datasets, all of them lasting 1000 s, but at varying TRs of 2 s (500 time points), 1 s (1000 time points) and 0.1 s (10,000 time points). Focusing only on the low-pass side, let us also assume the common cutoff frequency of 0.1 Hz, or one cycle every 10 s. At TR of 2 s, 40% of the DoF remain, because the Nyquist frequency is 0.25 Hz, and 0.1/0.25=0.4. In other words, out of 500 time points, 200 remain and 300 are lost. At TR of 1 s, only 20% of the DoF remain, i.e. out of 1000 time points, 200 remain and 800 are lost. Eventually, at TR of 0.1 s, only 2% of the DoF remain, as 0.1/5=0.02, i.e. out of 10,000 time points, 200 remain and 9800 are lost!! This demonstrates that when low pass filtering below 0.1 Hz, the effective TR becomes 5 s, leaving only 200 time points for 1000 s of data, regardless of the scanning TR. Hence, the cost of temporal filtering might be staggering for very short TRs. A more recommendable strategy is to include all the regressors into the design matrix, i.e. including the regressors of interest (either task-related or ROI time series in resting state), the nuisance regressors and the sine and cosine time series corresponding to the temporal filtering. By doing that, there will be a proper account of the number of degrees of freedom used to fit the data.

Summing up all these points, it is clear that giving a detailed report of the preprocessing pipeline and data analysis is very recommendable to enable a proper interpretation of the results, evaluate their flexibility in terms of the preprocessing choices (Carp, 2012a; 2012b), reduce any potential bias, and promote the reproducibility of results. This report could for instance follow the COBIDAS reporting guidelines (Nichols et al., 2015), although it might not be sufficient for certain non-standard approaches. A variety of simple but useful plots are available to illustrate the quality of fMRI data that facilitate the evaluation of denoising approaches (Power, 2016) and enable to identify the presence of remaining confounds that may affect the interpretation of the results (Burgess et al., 2016; Jo et al., 2013; Power et al., 2015; Power et al., 2016). We recommend the use and reporting of these plots. Ideally, it would be desirable to open the research to the community, i.e. sharing analysis code and data in public repositories, or implementing methods as open-source toolboxes. Similarly, when several methodological strategies have been evaluated, it would be advisable to inform about their corresponding results, and not only report the analysis that supports the hypothesis. Committing to these principles will help fMRI researchers to further improve our understanding of the influence of denoising and preprocessing in the results.

9. Conclusions

The fMRI signal is noisy; a complex amalgam of system-related noise, instrumental drifts and artefacts, movement-related effects, and intrinsic physiological fluctuations that obscure the neuronal related BOLD component of the signal which, despite being an indirect

measure of neuronal activity, we attempt to uncover in order to investigate how the brain functions while performing a task or at rest. For this ultimate goal, an extensive collection of denoising techniques has been developed since the early days of fMRI. These denoising techniques vary in the main target of application, either focusing on the removal of a specific type of noise (e.g. motion-related or physiological fluctuations), being sufficiently general in their scope (e.g. PCA- and ICA-based methods), or requiring non-standard features in data acquisition (e.g. methods based on the phase component of the signal or requiring multi-echo fMRI data). Due to the variability of signal confounds, algorithms available for denoising and the diversity of preprocessing choices, the researcher faces a difficult question about the most appropriate method for cleaning the signal. In this paper, we aimed to give a comprehensive review of existing denoising methods, from the very first approaches to the latest algorithms, briefly describing their principles and summarizing the pros and cons in their application. We noted that, in general, most of the approaches rely on nuisance regression for removing signal confounds. In that sense, since there is no prior knowledge of what is signal or noise, it is important to keep in mind that the signal variance removed by the nuisance regressors, and usually discarded, may also include highly structured information that can resemble the one typically coming from the clean signal (Bright and Murphy, 2015). Reducing signals of interest is therefore always a possibility, even with pure noise regressors, but this likelihood increases with a large number of nuisance regressors. Consequently, one should be cautious and sensible in the adequacy of the preprocessing and denoising methods applied to the signal, as well as consider the degrees of freedom lost in this process. In that sense, further refinement of models describing the causes of non-neuronal fluctuations and how they affect the BOLD signal are of paramount importance, particularly as the signal-to-noise ratio and the spatial and temporal resolutions improve with higher magnetic fields. Due to the inherent relationships between the causes of different non-neuronal fluctuations, further work would be valuable to determine whether, for instance, different denoising strategies are complementary or redundant and, therefore, causing an unnecessary loss in degrees of freedom and potentially removing signal of interest. These improved models will also stimulate the development of novel noise correction techniques, an investigation that should be performed by also comparing their performance with that of current approaches. In the end, the study of brain function well deserves an increased effort in improving the quality of the fMRI signal, which will eventually open the door to novel findings about the healthy and diseased brain.

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