Cleaning up the fMRI time series: mitigating noise with advanced acquisition and correction strategies

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The neuroimaging community has long been aware of the confounding influence of noise sources on quantifying and interpreting brain activity using fMRI. Because fMRI is a low signal-to-noise technique, advanced noise mitigation strategies are required to maximise its potential to uncover the true underlying workings of the brain. In this Special Issue, we explore the state of the art in this important field.

In typical fMRI experiments involving an external stimulus, statistical tests are applied to identify fMRI time-series that correlate significantly with the stimulus paradigm: we interpret these brain regions as being "activated" by the task. Over 20 years ago, the first concerns were raised about the contribution of head motion to the fMRI signal variance (Friston, Williams, Howard, Frackowiak, & Turner, 1996; Hajnal, Bydder, & Young, 1996). Tiny displacements of a millimetre or less could add random noise to the time-series and thus reduce statistical power in fMRI data. Even more challenging, if these movements were somehow correlated with the stimulus, they could drive false positive and false negative activations in an unpredictable way. Cardiac and respiratory signals were quickly identified as another source of noise (Glover & Lee, 1995; Noll & Schneider, 1994; Weisskoff et al., 1993) that could vary from person to person and potentially also become time-locked to the stimulus. Inflow effects and haemodynamic lags could cause mis-localisation of cortical activation (Glover, Lemieux, Drangova, & Pauly, 1996; Lee, Glover, & Meyer, 1995) and statistical methods needed optimisation for the formidable problem of multiple comparisons in typical fMRI datasets (Forman et al., 1995).

These early studies prompted Hajnal and colleagues to write (Hajnal, Bydder, & Young, 1995):

> *"The apparent simplicity and power of fMRI methods belie complexities that make the apparently simple step of ascribing detected signals to processes directly related to brain activation fraught with difficulties […] it may be unwise to continue with the same experimental design in the hope that one's own data are uncontaminated."*

Since these early revelations, fMRI researchers have had to regularly consider whether brain activation measures are biased by non-neuronal noise confounds. A new research field quickly emerged, developing techniques for "cleaning up" the fMRI time-series. Decades of development work in fMRI acquisition, signal processing, physiological modeling and statistical analysis have greatly improved our ability to accurately characterise brain activity using this promising and powerful imaging modality.

However, although many important denoising approaches have become standard practice, we now find ourselves once again faced with the possibility that results in the literature may be driven by noise confounds. This is partly due to advances in imaging methods: as scanner field strengths and spatial/temporal resolutions increase, and as new contrast mechanisms are exploited, noise correction methods should be re-evaluated and perhaps re-optimised. We are also acquiring unprecedented amounts of 'resting state' data, where no external stimulus is administered and instead we seek to characterise intrinsic neuronal fluctuations. In these data, we are even more dependent on accurate de-noising to identify the underlying 'activation' of interest, and existing de-noising methods are not yet sufficient. For example, subtle head motion, although much less destructive to the data than large movement artefacts, can drive apparent differences in resting state fMRI connectivity measures (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). Finally, the success of fMRI has resulted in an expansion of its applications: we need to rigorously assess whether our ability to differentiate and quantify signal and noise in fMRI data is altered in patient cohorts where physiology and behaviour may vary.

Such investment in cleaning up the fMRI time-series has additional benefits, providing tools for differentiating distinct sources of the combined BOLD-weighted signal variance. One researcher's "noise" is often another researcher's signal of interest, and new fields have emerged to study previously discarded aspects of fMRI variance. For example, the pulsatility of large arteries, typically a motion-related nuisance effect when studying nearby cortical activation, can also be examined as a marker for arterial compliance or stiffness (Warnert, Murphy, Hall, & Wise, 2014; Yan et al., 2016). The responsiveness of the vasculature to fluctuations in arterial CO_2 levels, commonly considered a source of respiration-related noise, can be purposefully probed using hypercapnia challenges in order to map cerebrovascular reactivity throughout the brain (Bright & Murphy, 2013). Thus, by *amplifying* noise, we can potentially gain new insight into healthy brain function and develop new imaging markers for identifying pathological changes.

In this Special Issue, we explore the current understanding of fMRI noise, and current best practices for reducing the impact of noise on fMRI results. In order to ultimately achieve robust measures of brain activation, the impact of noise must be considered at all stages of the imaging experiment, from scan acquisition to group level statistics.

The issue opens with a scene-setting paper by Liu that reviews various possible sources of noise and the MR physics mechanisms by which they influence the fMRI BOLD signal (Liu, 2017). The challenge of distinguishing signals-of-interest from noise is discussed, indicating the potential pitfalls when cleaning up fMRI time series.

It is a self-evident statement that the best way to arrive at clean fMRI time-series is to acquire non-noisy data in the first place. Wald and Polimeni examine the effects of image acquisition parameters that are critical in determining the important ratio of physiological to thermal noise in fMRI time-series (Wald and Polimeni, 2017). Several acquisition strategies are proposed that will help reduce false positive rates caused by spatially structured physiological noise. Higher field strengths allow for greater spatial specificity which may introduce even more noise, especially when parallel imaging techniques are used. Vu and colleagues compare numerous spatial resolutions and demonstrate that high resolution whole-brain fMRI images can be achieved while maintaining useful contrast-to-noise ratios (Vu, et al., 2017). When addressing motion-related noise in fMRI, retrospective motion correc- tion techniques can be useful but are unable to correct for intra-volume movement and spin history effects. Zaitsev and colleagues investigate the application of prospective motion correction combined with dynamic distortion correction to overcome these limitations in fMRI data (Zaitsev, et al., 2017). The last two papers in this section describe contrast mechanisms that are complementary to BOLD that may alleviate some noise concerns but may also introduce others. An overview of the arterial spin labelling (ASL) and vascular space occupancy (VASO) methods is presented by Donahue and colleagues (Donahue, et al., 2017). This paper focuses on the appropriate post- processing and experimental acquisition strategies that reduce sensi- tivity to noise and unintended signal sources that are prominent in these techniques. Kundu and colleagues review the multi-echo fMRI BOLD acquisition approach as a way of separating signal from noise (Kundu, et al., 2017). The paper focusses on recent techniques that combine multi-echo data with spatial ICA to classify signal components as neural-related or noise-related, thus boosting statistical power.

Some noise is perhaps unavoidable; however, if sources of noise can be monitored, they can potentially be removed in post-processing. Four papers address the issue of monitoring relevant noise sources during fMRI acquisitions. The paper by Bulte and Wartolowska considers the practicalities of monitoring physiology during fMRI acquisitions, how to acquire accurate traces, and how to incorporate them into a processing pipeline (Bulte and Wartolowska, 2017). Moreover, con- sideration is given to scans with cerebrovascular stimuli, where standard analysis techniques could be detrimental. Bollmann and colleagues investigate the role of magnetic field fluctuations as a confound in fMRI and demonstrate that they can be monitored using field probes and effectively addressed by retrospective data correction techniques (Bollmann, et al., 2017). Similar probes can be used to measure physiological noise during scanning: Gross and colleagues demonstrate a touch-free method for measuring cardiac and respira- tory signals using magnetic detection with NMR field probes (Gross, et al., 2017). It is demonstrated that these versatile probes could be integrated into the patient table, enabling routine, hassle-free record- ing of these noise sources. Finally in this section, Abreu and colleagues demonstrate the generation of a physiological noise model using concurrent ECG recordings to remove both cardiac and respiratory noise (Abreu, etal., 2017). The impact of this noise correction outper- forms ICA-based correction and is shown to improve the mapping of epileptic networks.

Much of the work in the literature to date has focussed on assessing and removing fMRI noise during post-processing. Caballero-Gaudes and Reynolds comprehensively summarise the current state-of-the-art for cleaning fMRI BOLD signals in post-processing (Caballero-Gaudes and Reynolds, 2017). Advantages and limitations of the many methods are outlined and compared. Power presents a short, practical “how-to” paper that describes a plot used to assess fMRI data quality and to determine the effectiveness of post-processing strategies (Power, 2017). Nuisance regression using a General Linear Model (GLM) is a widely used method to remove noise from fMRI data. Bright and colleagues examine the statistical assumptions and requirements of the GLM in the context of fMRI noise removal (Bright, et al., 2017). Numerous recommendations are made to help researchers achieve valid statistical inference and improve noise models for cleaning resting state fMRI time series. The use of the global signal in a GLM as a noise removal technique for resting state fMRI has generated much controversy; motivating new processing strategies but also generating significant confusion and contradictory guidelines. Murphy and Fox, the authors of two earlier papers that came to conflicting conclusions, work towards a consensus regarding global signal regression (GSR), highlighting points of agreement between the two camps (Murphy and Fox, 2017). GSR is one of the numerous strategies suggested to deal with motion artefacts that are particularly problematic in functional connectivity studies, conflating results. Ciric and colleagues system- atically evaluate many of the confound regressions that have been proposed to deal with this important issue (Ciric, et al., 2017). It is suggested that different strategies may be appropriate in different scientific contexts. Another approach to post-processing noise removal is independent component analysis (ICA) which requires classification of components into signal and noise. Griffanti and colleagues present another practical “how-to” guide on classifying single-subject indepen- dent components (Griffanti, et al., 2017).

Reliable single-subject fMRI is key if the technique is to be useful in diagnostic imaging and investigations of individual differences. Gonzalez-Castillo and colleagues investigate the temporal and spatial distributions of within-subject variability of fMRI task responses (Gonzalez-Castillo, etal., 2017). Sources of variability that are usually treated as noise show that different brain regions will have different natural levels of test-retest reliability. At the group level, residual artefacts after noise removal can lead to violations of the assumption that variance is constant across subjects in a group level model. In the paper by Mumford, the strategy often used to deal with this issue, robust regression, is shown to lead to inflated Type 1 errors (Mumford, et al., 2017). Comparisons are made with other approaches and situations in which robust regression works or doesn't work are described.

The final four papers of this Special Issue deal with situations in which extra care is required when considering fMRI noise removal. Fassbender and colleagues examine noise in paediatric populations (Fassbender, et al., 2017). Imaging children, especially those with developmental disorders, is very challenging due to problems with hyperactivity, anxiety and an inability to perform the task and maintain attention. In this paper, with years of experience imaging such challenging populations, the authors describe the practical strategies they use in their lab to minimise associated noise issues when conducting fMRI experiments. At the opposite end of the lifespan, care must be taken as many noise correction methods are optimised on young adults. Churchill and colleagues compare optimised pipelines between young and older cohorts and demonstrate a significant benefit of adaptive pipeline optimisation (Churchill, et al., 2017). Spinal cord fMRI is an area that is expanding in popularity. However, the spinal cord is particularly difficult to image for many reasons, including the large contribution of physiological noise. Eippert and colleagues describe approaches to deal with spinal cord specific noise issues at both the acquisition and post-processing stages (Eippert, et al., 2017). Finally, Keilholz and colleagues review different types of noise and non- neuronal contributions to the BOLD signal in animal studies (Keilholz, et al., 2017). These studies can be particularly prone to noise because of alterations in neural activity, vascular tone and neurovascular coupling caused by use of anaesthesia that affect intra- and inter-animal variability. Potential mitigations of these issues and future outlooks are discussed.

In putting together this issue, we do not intend to bring the de- noising question to a close, or to prescribe what de-noising strategy should be used or is sufficient. The methods by which a given study will address fMRI noise confounds will ultimately depend on the hardware available, the cohort under consideration, and other practical aspects that will always vary across the literature. Instead, we hope to raise awareness of the challenges associated with differentiating signal from noise in fMRI data, and simultaneously raise standards for de-noising practices across the imaging community.

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