Data Analysis: potential pitfalls and sources of error

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Multi-centre trials offer the ability to obtain larger amounts of MRI data per unit time than single-centre studies, and they are therefore very attractive for setting up large population studies. Typically, clinical studies aim at comparing some MRI-derived quantitative indices of pathology across groups of subjects, and/or at correlating them with other parameters, such as clinical scores. The process of quantification of MRI-derived quantities, however, starts at the acquisition of the raw data, followed by a long pipeline of image processing steps, each containing potential sources of bias. This talk reviews some of the pitfalls associated with the most commonly used methods of analysis for quantitative MRI.

Typically, quantitative MRI techniques fit a model of the dependence of the MR signal on a physical process to a number of MRI measurements obtained at different settings of the acquisition pulse sequence. For the purpose of this talk, the steps of the analysis pipeline will be grouped into 1) pre-processing, including any manipulation of the data prior to model fitting; 2) model fitting and derivation of voxel-wise parameters; 3) strategies for data extraction and between-group comparison.

While most of the processing steps discussed here can be applied to any kind of quantitative image, there is a special focus on diffusion MRI, for two reasons: it is the most popular imaging techniques for assessing brain tissue integrity, being at the same time particularly vulnerable to data analysis pitfalls.

1. Pre-processing of data

Pre-processing typically includes all the steps needed to compensate for involuntary motion between scans (i.e., image co-registration), and to correct for all kinds of artefacts that might occur during acquisition. It is important to highlight that confounds such as the effects of susceptibility and eddy currents strongly depend on the hardware and software characteristics of the scanner used to collect the images, and thus they will differ between data acquired at different sites. While the purpose of pre-processing is to minimise these confounds, it will be shown how using off-the-shelf correction programs, without understanding of their shortcomings, might lead to substantial errors. Diffusion MRI data acquired with echo-planar readout, for example, are typically affected by susceptibility induced distortions. These artifacts can severely affect the output of tractography (1) and therefore it is desirable to compensate for them. A relatively simple solution to susceptibility distortion consists of measuring the B0 field and applying a retrospective correction to the distorted data (2). Unfortunately, susceptibility-induced distortions are non-linear, and it is possible that the signal intensity from neighbouring voxels collapses into a single voxel, due to the rapid susceptibility variation across the object. In this case unwarping becomes an ill-posed problem and can lead to unexpected results. Among the other topics covered, the importance of rotating the B matrices (3) when applying image registration to diffusion data, and the consequences of (badly) correcting for eddy-current effects.

2. Model fitting and derivation of voxel-wise parameters

Once data have been corrected for motion and distortions, they are ready for voxel-wise model fitting. Most models of signal behaviour are non-linear, although some of them can be taken into a linear framework (e.g., diffusion tensor, T2/T2* relaxation, etc). In the latter case the fitting is simplified and it can be implemented very quickly. Non-linear regression methods are subject to the risk of ending in a local instead of the global minimum, and therefore of yielding a biased estimate. Standard linear methods, on the other hand, can enhance the noise in some areas of the brain. Because of their different performance, it is important to recognise that results computed with different regression methods cannot be compared.

Depending on the specific technique, the output of the fitting might not be the quantity of interest (e.g., in diffusion tensor MRI, one typically aims at extracting scalar invariants rather than the tensor itself), and further computation is thus required. Even these relatively straight-forward calculations are subject to pitfalls (e.g., spatially heterogeneuous effect of noise).

3. Strategies for data extraction and between-group comparison

Once the parametric maps of interest have been computed, it may be necessary to extract summary measures, in a format suitable for a statistical comparison, from either the whole brain or specific anatomical locations. For this purpose three alternative approaches are available: region of interest (ROI), histogram and voxel-based (VB) analysis.

ROI analysis is strongly operator dependent, and thus typically characterised by a large inter-rater variability. To minimise variability, manual positioning of ROIs should be done by a single observer, although some intra-rater variability is also expected. The choice of the reference image used to draw the ROI can also affect the results: if ROIs are defined directly on the parametric map of interest, the intensity on the map might spuriously influence the position of the ROI boundaries.

Histogram analysis reflects global changes, testing across the whole brain, and it is thus particularly indicated when dealing with a diffuse disease. Manual intervention is less critical than in ROI analysis, and thus this method of analysis tends to be more reproducible. Nevertheless, this approach is also vulnerable to confounds arising at the critical step of the removal of the tissue of no interest (typically CSF). This confound may be particularly evident when the subjects in one group are more likely to be atrophic than those in the other group.

Voxel-based (VB) analysis is becoming more and more popular as a method of analysing quantitative images because it is highly automated, and it conjugates some of the advantages of histogram analysis, namely the possibility of analysing the whole brain with no a priori hypothesis on the location of pathology, with the spatial specificity of ROI analysis. However, the number of options available for pre-processing the data and setting up the comparison yield a huge variety in the results obtained by different groups in similar experiments. Some of the factors affecting the outcome (spatial normalisation, smoothing kernel, statistical analysis, etc) will be discussed in detail.

Conclusions

The take-home message is that, when comparing results between centres, it is important to establish not only what acquisition was used, but also what processing steps were undertaken. Finally, although it often is tempting to trust the output of the many automated tools for data analysis which have nowadays become available, it is important to ensure the

reliability of these algorithms with the images available for the analysis, it is mandatory to verify the result of each step through-out, and it is desirable to be fully aware of the limitations and the assumptions behind them.

References

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