MRM Tutorial

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1 Analysing repeated measurements

Repeated measurement designs are fairly common in neuroimaging. Examples include longitudinal studies, where individuals are followed-up at multiple time points, or studies using neurocognitive paradigms with multiple experimental conditions. In each case the pertinent point is that the individual subjects are measured more than once. It is therefore necessary that any form of group-level statistical modelling is able to accommodate the correlation between the measurements taken from the same individual. In this tutorial I will cover the analysis of these forms of designs using a multivariate general linear model (GLM) approach, as implemented in the Multivariate and Repeated Measures (MRM) toolbox available from `http://www.click2go.umip.com/i/software/mrm.html`.

1.1 The data

The data for the first example is taken from an investigation into the effects of a history of major depressive disorder on normal ageing. There are two between-subject variables, `Age` (`older` vs `younger`) and `Diagnosis` (`remitted depression` vs `controls`). Each subject from the 4 groups participated in an emotional memory task where they were shown blocks of images. These blocks were either `negative`, `positive`, or `neutral`. Because all subjects were shown all images we therefore have a single within-subject (repeated measurement) variable of `Condition` (`negative` vs `positive` vs `neutral`). Our aim will be to analyse all these conditions in a single group-level repeated-measures model.

For this example the data have already been pre-processed. As MRM is designed for use in the summary-statistic approach to group-level modelling of neuroimaging data the 1st-level models have also already been fit for each subject. In each case the three conditions of the memory task were modelled (`negative`, `positive`, `neutral`) with rest periods left as implicit baselines. The parameter estimates for each condition (as the implicit comparisons with rest) are therefore those values taken through to the group level. As such, each subject has three parameter estimate images from the three conditions. These will be modelled together with the group structure in the single MRM repeated measures model.

1.2 Specifying the model

Once MRM has been added to the MATLAB path you can launch it by typing `mrm` at the command prompt. The first window you will see will be the launcher, shown in **Figure 1**, containing buttons for the main MRM tools.

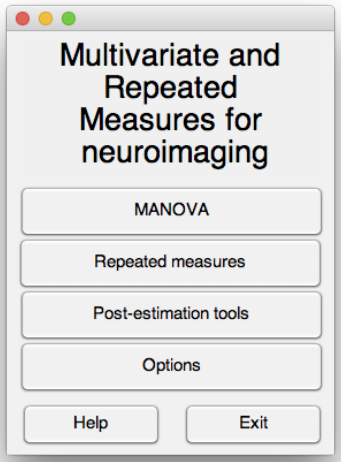


Figure 1 – The MRM launcher window

To specify a repeated measurement model click the `Repeated measures` button. This will launch the model specification interface shown in **Figure 2**. The main idea here is to work from the top of the window to the bottom, filling in all the model details as you go. Unlike SPM, where you specify the type of GLM you wish to use (e.g. two-sample t-test, one-way ANOVA, paired-samples t-test etc.), the approach here is more generic, based simply on indicated the number of *within-subject* and *between-subject* factors in the design.

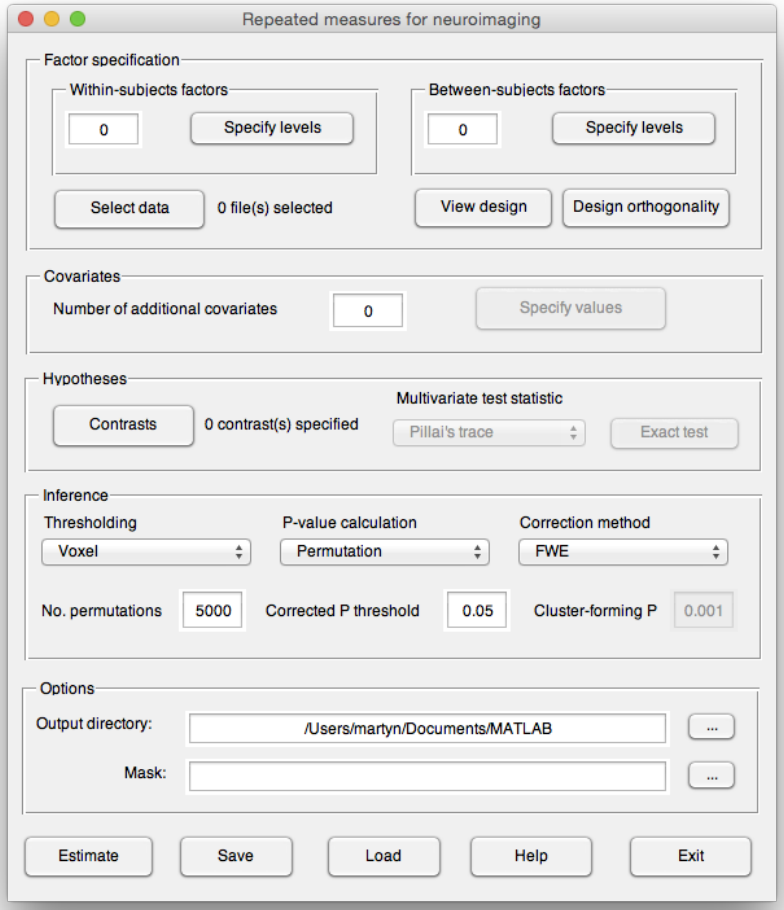


Figure 2 – The MRM repeated measures model specification

1.2.1 Factorial specification

In our dataset we have a single within-subjects factor (the *condition* of the task) as well as two between-subject factors (the *diagnosis* groups and the *age* groups). To specify a model for these data we first change the number of within-subject factors from 0 to 1 and click the `Specify levels` button. This will open the interface shown in **Figure 4** where we can name the factors and indicate the number of levels of each. Because we only indicated one factor we get one row to enter the name of the factor and the number of levels. Here we name the factor `Condition` and indicate that there are 3 levels (for the 3 conditions of the task). We then need to provide labels for each level. Clicking on the `Set labels for selected factor` button will launch a window containing rows for providing labels for the levels of the factor. As shown in **Figure 4**, in this example we use the name of the picture conditions. Once entered press `Done` on the labels window, and `Done` on the factor specification window.

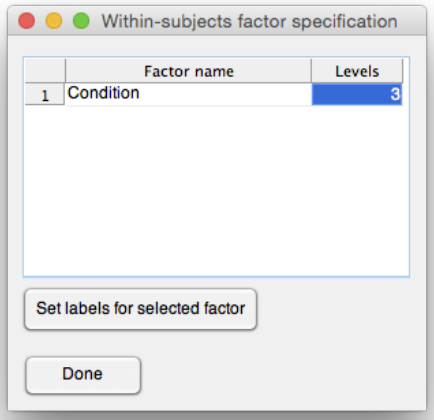


Figure 3 – The factor name and levels window

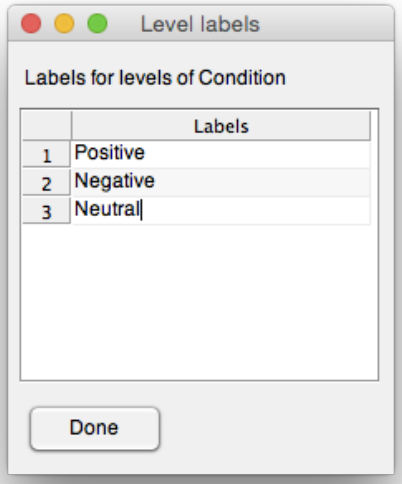


Figure 4 – Labelling the within-subjects factor

We use a very similar process for the between-subject factors. This time we have two factors, *diagnosis* and *age*, and so we enter 2 in the the `Between-subject factors` box. When specifying the factor names we now have two rows in which to enter the names and levels. When specifying the labels for the levels we must make sure we have the correct row selected by clicking on it before selecting the `Set labels for selected factor` button. For the `Diagnosis` factor we enter `Control` and `Remitted` as labels for the levels. For the `Age` factor we enter `Older` and `Younger` as the levels. This is shown in **Figure 5**

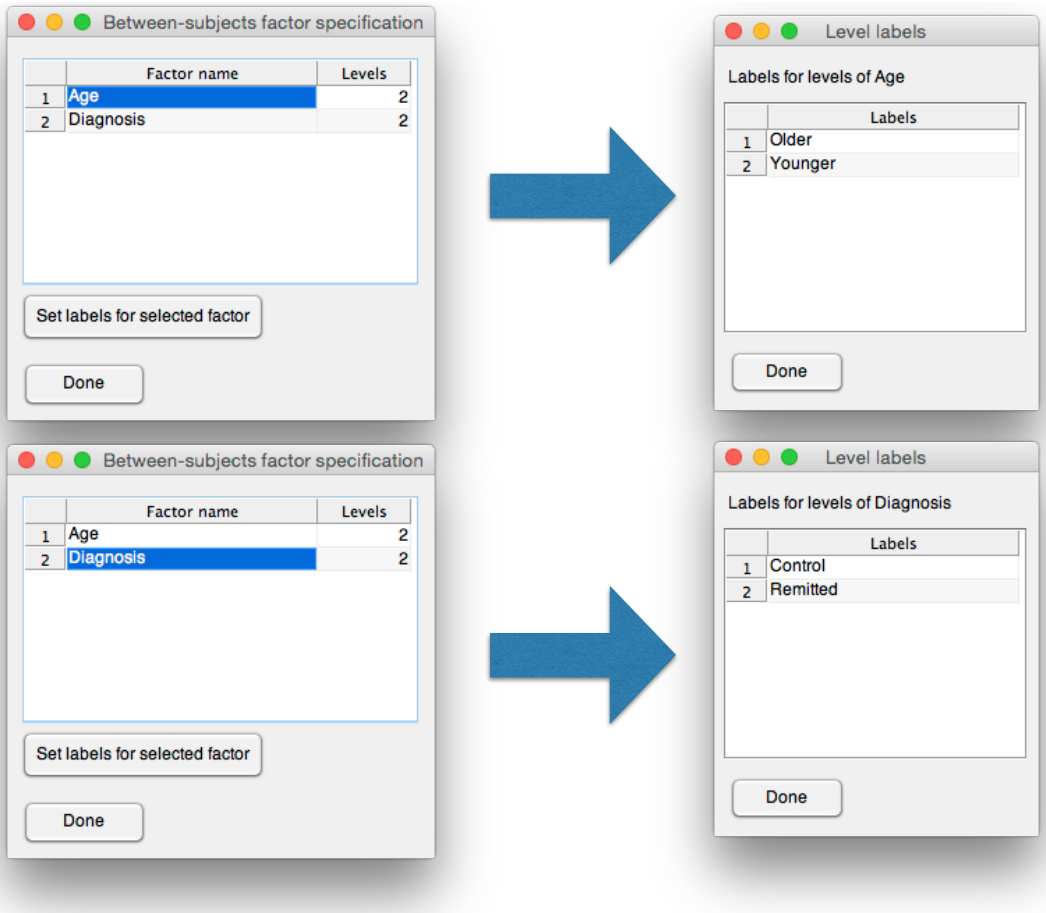


Figure 5 – Specifying the between-subjects factors

1.2.2 Selecting the data

Once the factorial structure of the data has been specified we can select the scans. MRM is designed to only work with single NifTi files (those with a *.nii extension). If your files are in the old Analyze format (separate *.hdr and *.img files) they will need converting before they can be used. Pressing the `Select data` button will open the dialog box in **Figure 6**. Here the structure of the design is presented in a list organised by each dependent variable and then each cell of the between-subjects design. This interface makes the multivariate nature of the model clear as we are simply specifying the data to coincide with each of the individual linear models that make up the multivariate specification. Knowing this should allow for the data to be organised into a structure that will make selecting all the files as easy as possible.

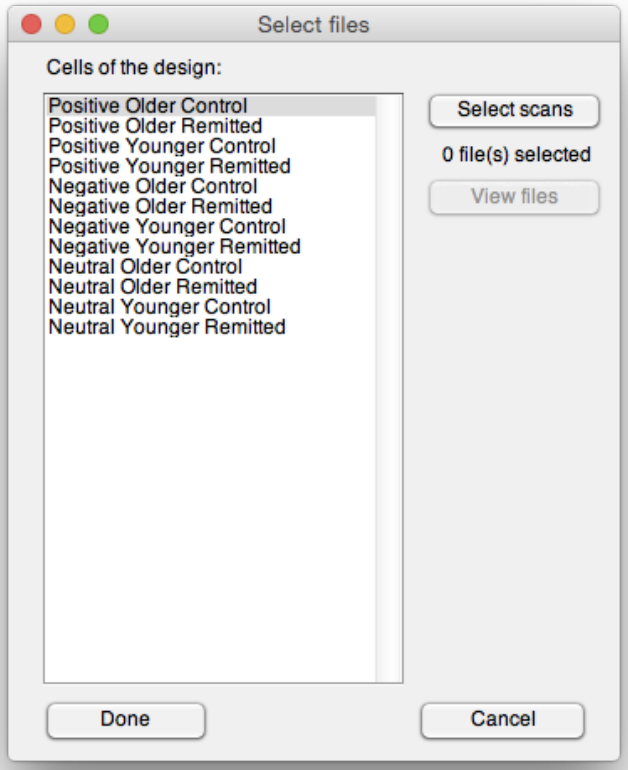


Figure 6 – Interface for selecting the scans in the example design

For each combination of factor levels we must selected the corresponding scans by pressing the `Select scans` button. For example, the first elements of the list corresponds to `Positive Older Control`. As such, we need to select all the images from the SPM 1st-Level analysis for the older adult controls corresponding only to the `Positive` picture condition. For each entry on the list we must select all the scans at once. The number of files will then be indicated under the `Select scans` button. The file paths for all the scans can also be viewed by pressing the `View files` button. Importantly, missing data across the repeated measurements is not allowed. For example, the number of scans for `Positive Older Control` and `Positive Older Remitted` *can* differ, however, the number of scans for `Positive Older Control` and `Neutral Older Control` cannot. In the event that this occurs a warning will be given. Once all the scans are selected press the `Done` button and a count of the total number of files is given next to the `Select data` button. This will correspond to $n \times t$, where n is the number of subjects and t is the number of repeated measurement conditions. In our example there are 55 subjects and 3 conditions, leading to 165 files selected in total.

1.2.3 Design visualisation and orthogonality

Once the files are selected we can view the design visualisation by pressing the `View design` button. This is shown in **Figure 7**. For users of other neuroimaging software

this visualisation should be familiar. On the right of the figure is a greyscale image of the design matrix $\mathbf{X}$. For all MRM models a cell-means coding approach is used such that the columns correspond to the cell means of the design. To the left of the design matrix is a visualisation of the $n \times t$ outcome matrix $\mathbf{Y}$. Here the multivariate nature of $\mathbf{Y}$ is depicted by providing shaded columns corresponding to the multiple dependent variables. In a repeated measures model these columns are the result of the highest-order interaction between the within-subject factors. In the example shown in **Figure 7** we only have a single within-subject factor and as such the columns are simply the levels of that factor. In general, the design visualisation attempts to depict the $\mathbf{Y} = \mathbf{X}$ part of $\mathbf{Y} = \mathbf{XB} + \mathbf{E}$.

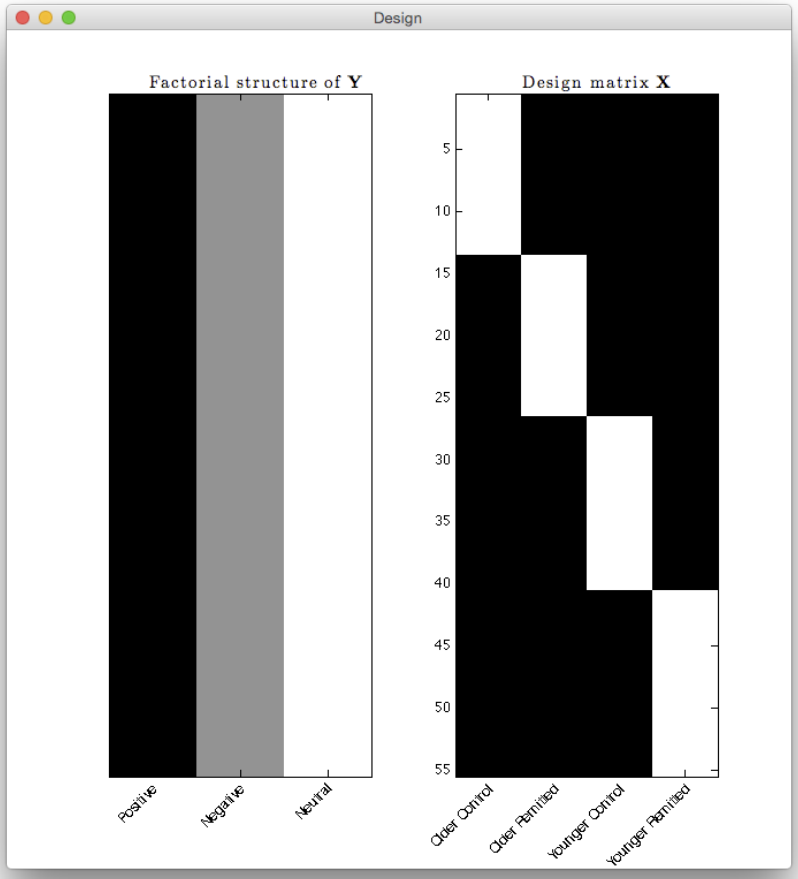


Figure 7 – The multivariate design visualisation

The design orthogonality button can now also be used. Here a visualisation is provided to help identify any issues with multicollinearity in the design, using an identical scheme to SPM. Here the absolute value of the cosine of the angle (θ) between the vectors given by the columns are shown. For the columns to be orthogonal they should be at 90°, giving $\cos\theta = 0$. Perfectly collinear vectors (i.e. 0° or 180°) provide $|\cos\theta| = 1$. As shown in **Figure 8**, the diagonal of this figure indicates perfect collinearity between each column and itself. Ideally all the off-diagonal elements should be white, indicating $\cos\theta = 0$. Anywhere coloured grey

indicates some degree of collinearity between the indicated vectors and should be investigated.

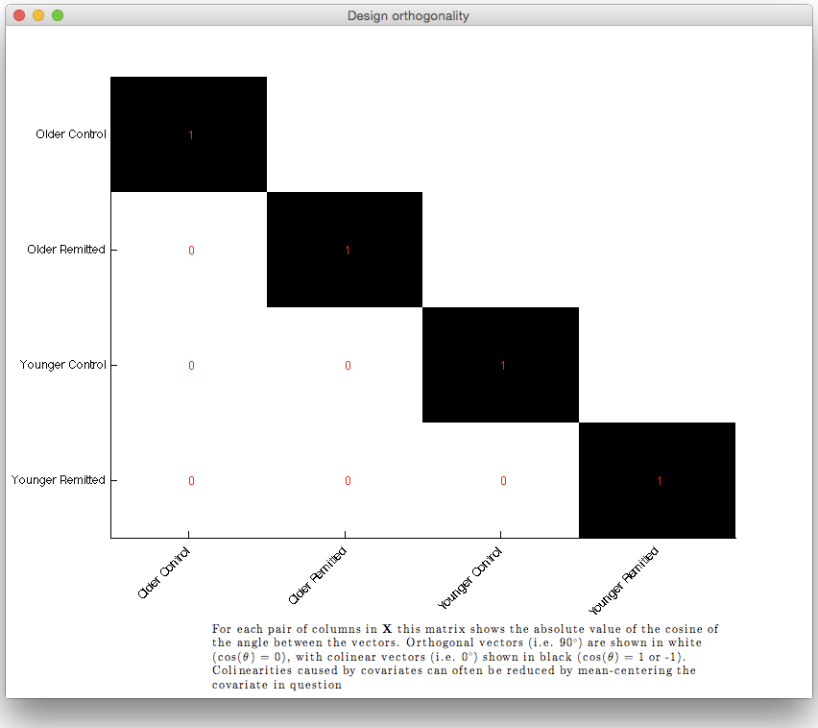


Figure 8 – The model orthogonality visualisation

1.2.4 Covariates

The final option in specifying the design of the model is to add any number of additional covariates to the end of the design matrix. In those cases where no between-subject factors are given the design matrix will consist of only a constant. Addition of covariates turns this specification into a multivariate regression, though this is probably more sensibly specified through the `MANOVA` module (see the later section on multimodal models). Covariates within the `Repeated measures` module really serve the purpose of a repeated-measures ANCOVA model (specified here as a MANCOVA). In our example we are not using any covariates, but the procedure is relatively straightforward. The number of covariates is specified in the box seen in **Figure 2**. Names are then entered and then the values of the covariates are provided either manually, or by copying and pasting from an external program. By default any covariate is automatically mean-centred (by subtracting the mean of the covariate from each element). This can be prevented by un-ticking the `Mean centering` option. As a general warning, it is always important to consider the suitability of any covariate for the design at hand, with proper consideration given before adding extra columns to the design (see the Miller & Chapman 2001 paper on 'Misunderstanding Analysis of Covariance' for more on this issue).

In the multivariate specification covariates represent only *between-subject* values. As such there should be a single value on the covariate per-subject (e.g. age,

weight, IQ etc.). As with the traditional univariate analyses the parameter estimate associated with the covariate can be interpreted as the slope of the regression line between the covariate and the measured outcome in $\mathbf{Y}$. In the multivariate framework a slope parameter is estimated for each column of $\mathbf{Y}$. In our current example, if we wished to enter IQ as a covariate then we would estimate three slopes indicating the individual relationships between the covariate and the three conditions of the task. We could then compare the slopes to assess how the estimated relationship between IQ and the BOLD signal changes depending on the condition of the task. It is also possible to split the covariate such that different slopes are estimated for each between-subject grouping. This is done manually in a fashion akin to FSL. See the GLM wiki on the FMRIB site for more information on this: `http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/GLM`.

Addition of continuous covariates into these designs can cause issues with collinearity. For designs with only factors, orthogonality of the columns of $\mathbf{X}$ is guaranteed by the cell means model. As such the orthogonality visualisation is not particularly useful (such as **Figure 8** above). For designs that contain covariates this feature is more useful. Generally speaking any issues that arise after adding covariates can often be resolved by mean-centring the covariate in question (this is the default in MRM). For covariates where different slopes are desired for different groupings of the data the general advise is to centre the covariate *before* splitting it. In these cases the centring option should be turned off.

1.3 Contrasts

Once we have fully specified the design we can then turn to the hypothesis tests we wish to perform. As with univariate neuroimaging approaches, this is done via the specification of contrasts of the parameter estimates. The use of such of an approach in the multivariate framework does, however, differ in some important ways. Although possible to get MRM to automatically generate the standard ANOVA contrasts, it is important to understand the scheme being used in order to fully take advantage of the flexibility of this approach. This will also be important when we come to plotting results. As such, we will take a short detour into explaining this hypothesis testing scheme before returning to the specification of these contrasts in MRM. Those familiar with the multivariate scheme can skip ahead to **Section 1.3.2**.

1.3.1 Contrast theory

In the univariate GLM

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$$

the parameter vector $\boldsymbol{\beta}$ consists of a single column. Assuming a simple 2×2 ANOVA model the values of these parameters are the cell means of the design, and can be represented as

$$\boldsymbol{\beta} = \begin{bmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{bmatrix}$$

where μ_{11} is the mean from the first level of the first factor and the first level of the second factor, μ_{12} is the mean from the first level of the first factor and the second

level of the second factor etc. In order to test hypotheses about these parameters we can provide a contrast $\mathbf{L}$, encoding a linear combination of the parameters to test against 0. For example, a main effect of the first factor can be given by

$$\mathbf{L}\boldsymbol{\beta} = \begin{bmatrix} 0.5 & 0.5 & -0.5 & -0.5 \end{bmatrix} \begin{bmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{bmatrix} = \frac{1}{2}(\mu_{11} + \mu_{12}) - \frac{1}{2}(\mu_{21} + \mu_{22})$$

which is simply the average of the first two means minus the average of the second two means. Because in practise we generally do not know the true value of $\boldsymbol{\beta}$ we can only construct a contrast of parameter *estimates* (denoted $\hat{\boldsymbol{\beta}}$) based on a sample. As such we use $\mathbf{L}\hat{\boldsymbol{\beta}}$ to construct a test statistic that accommodates our uncertainty about the estimation of $\boldsymbol{\beta}$. Typically in neuroimaging this is a t-statistic, but more generally can be considered in terms of the F-statistic given by

$$F = \frac{(\mathbf{L}\hat{\boldsymbol{\beta}})'[\mathbf{L}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{L}'](\mathbf{L}\hat{\boldsymbol{\beta}})}{r\hat{\sigma}^2}$$

where $\hat{\sigma}^2$ is the estimated residual variance (the mean squared error), and $r = \text{rank}(\mathbf{L})$.

In the multivariate GLM

$$\mathbf{Y} = \mathbf{X}\mathbf{B} + \mathbf{E}$$

the multivariate parameter matrix $\mathbf{B}$ consists of multiple columns. Assuming again a 2×2 ANOVA model, if we actually measured each subject twice and used those two time-points as separate outcome vectors in $\mathbf{Y}$ our model would be a $2 \times 2 \times 2$ repeated measures design, and our multivariate parameter matrix $\mathbf{B}$ would be

$$\mathbf{B} = \begin{bmatrix} \mu_{111} & \mu_{112} \\ \mu_{121} & \mu_{122} \\ \mu_{211} & \mu_{212} \\ \mu_{221} & \mu_{222} \end{bmatrix}$$

where μ_{111} is the mean from the first level of the first factor and the first level of the second factor *at timepoint 1*, μ_{112} is the mean from the first level of the first factor and the first level of the second factor *at timepoint 2* etc. The rows of $\mathbf{B}$ therefore reflect the between-subject parameters, whereas the columns reflect the within-subject parameters. Applying $\mathbf{L} = \begin{bmatrix} 0.5 & 0.5 & -0.5 & -0.5 \end{bmatrix}$ to $\mathbf{B}$ is then not enough to specify a full hypothesis because the matrix $\mathbf{L}$ only acts on the between-subject parameters. As such, $\mathbf{LB}$ would provide *two* values in the same row, the main effect of the first factor at time point 1 *and* the main effect of the first factor at time point 2. We therefore introduce a second contrast matrix (denoted $\mathbf{M}$) to act exclusively on the within-subject parameters. As such, the multivariate hypothesis scheme is not to test

$$\mathbf{L}\boldsymbol{\beta} = \mathbf{0}$$

rather it is to test

$$\mathbf{LBM}' = \mathbf{0}$$

where $\mathbf{0}$ is a column vector of zeros, such that we can use

$$\begin{aligned}\mathbf{LBM}' &= \begin{bmatrix}0.5 & 0.5 & -0.5 & -0.5\end{bmatrix}\begin{bmatrix}\mu_{111} & \mu_{112}\\ \mu_{121} & \mu_{122}\\ \mu_{211} & \mu_{212}\\ \mu_{221} & \mu_{222}\end{bmatrix}\begin{bmatrix}0.5\\ 0.5\end{bmatrix}\\ &= \begin{bmatrix}(\mu_{1.1} - \mu_{2.1}) & (\mu_{1.2} - \mu_{2.2})\end{bmatrix}\begin{bmatrix}0.5\\ 0.5\end{bmatrix}\\ &= \frac{1}{2}(\mu_{1.1} - \mu_{2.1}) + \frac{1}{2}(\mu_{1.2} - \mu_{2.2})\end{aligned}$$

giving us the main effect of the first factor averaged over the within-subjects factor. Here the 'dot' notation indicates a subscript averaged over.

In general this scheme is very flexible. In order to specify a between $\times$ within interaction we can use e.g. $\mathbf{L} = \begin{bmatrix}0.5 & 0.5 & -0.5 & -0.5\end{bmatrix}$ and $\mathbf{M} = \begin{bmatrix}1 & -1\end{bmatrix}$, simply a between-subject main effect and a within-subject main effect. Similar to the between-subject case, the within-subject main effect is given by $\mathbf{L} = \begin{bmatrix}0.25 & 0.25 & 0.25 & 0.25\end{bmatrix}$ and $\mathbf{M} = \begin{bmatrix}1 & -1\end{bmatrix}$. Finally, the 3-way interaction is $\mathbf{L} = \begin{bmatrix}0.5 & -0.5 & -0.5 & 0.5\end{bmatrix}$ and $\mathbf{M} = \begin{bmatrix}1 & -1\end{bmatrix}$, a combination of a 2-way between-subject interaction and the main effect of the within-subject factor. This scheme also makes follow-up tests very easy to specify. For example, in the case of a significant between $\times$ within interaction the simple main effects of the first factor at the levels of the within-subject factor are given by $\mathbf{L} = \begin{bmatrix}0.5 & 0.5 & -0.5 & -0.5\end{bmatrix}$ with $\mathbf{M} = \begin{bmatrix}1 & 0\end{bmatrix}$, and $\mathbf{L} = \begin{bmatrix}0.5 & 0.5 & -0.5 & -0.5\end{bmatrix}$ with $\mathbf{M} = \begin{bmatrix}0 & 1\end{bmatrix}$.

Insofar as the tests of these contrasts are concerned we define two *sums of squares and crossproducts* (SSCP) matrices, one for the hypothesis (SSCP_H) and one for the error (SSCP_E). These are analogous to the numerator and denominator values for the univariate F, and are given by

$$\begin{aligned}\text{SSCP}_H &= (\mathbf{L}\hat{\mathbf{B}}\mathbf{M}')'[\mathbf{L}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{L}'](\mathbf{L}\hat{\mathbf{B}}\mathbf{M}')\\ \text{SSCP}_E &= \mathbf{M}'(\hat{\mathbf{E}}'\hat{\mathbf{E}})\mathbf{M}\end{aligned}$$

Once formed we can then use these matrices to construct tests statistics. In each case the idea is to reduce the multivariate information in SSCP_H and SSCP_E to a single scalar value. In general there are 4 standard ways of doing so

$$\begin{aligned}\text{Pillai's trace} &= \text{trace}[\text{SSCP}_H(\text{SSCP}_H + \text{SSCP}_E)^{-1}]\\ \text{Wilks' } \Lambda &= \frac{\det(\text{SSCP}_E)}{\det(\text{SSCP}_H + \text{SSCP}_E)}\\ \text{Hotelling-Lawley trace} &= \text{trace}[\text{SSCP}_H\text{SSCP}_E^{-1}]\\ \text{Roy's largest root} &= \frac{\lambda^\star}{1 + \lambda^\star}\end{aligned}$$

where $\lambda^\star$ is the largest eigenvalue of $\text{SSCP}_E^{-1}\text{SSCP}_H$.

The relative merits of these statistics will not be covered here (have a look at Rencher & Christensen, 2012). However, there are some points of note. Firstly, an F approximation exists for all these statistics, and as such we always find ourselves on familiar ground when using the multivariate hypothesis testing approach. However, because of this we cannot use one-sided tests. Secondly, there are numerous cases where the F values provided are exact, and as such the statistics above do not differ

in the F-values they provide. When they do differ, Pillai's trace is generally the most conservative (read as the *safest* approach), whereas Roy's largest root is generally the most liberal (read as the most *unsafe* approach). Finally, there is good evidence to suggest that permutation approaches to calculating p-values may generally be the best bet in the multivariate framework as we do not need to rely on asymptotic F-approximations and their (potentially) dubious parametric assumptions. This is particularly true in neuroimaging where such assumptions are needed *at every voxel*. We will cover permutation approaches in MRM later.

1.3.2 Specifying contrasts in MRM

In MRM contrasts can be specified by clicking the `Contrasts` button to launch the interface shown in **Figure 9**.

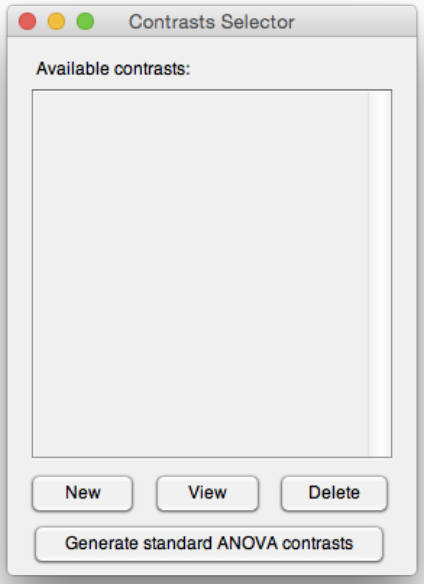


Figure 9 – The interface for the currently available contrasts

Clicking on the `Generate standard ANOVA contrasts` button will produce a set of contrasts for the specified factorial design. This should be fine up to a 4-way interaction. Anything beyond that will need specifying yourself (a warning will be given). You can view and edit any of these contrasts by pressing the `View` button, and delete any using the `Delete` button. For the purposes of this tutorial we will walk through specifying the contrast for the `Main effect of Age`.

Pressing the `New` button will launch the interface shown in **Figure 10**. As explained in **Section 1.3.1**, the hypothesis testing scheme in the multivariate GLM is given by testing $\mathbf{LBM}' = 0$, for a between-subject hypothesis coded in $\mathbf{L}$ and a within-subject hypothesis coded in $\mathbf{M}$. $\mathbf{L}$ will therefore act on the *rows* of the parameter matrix $\mathbf{B}$, and $\mathbf{M}$ will act on the columns. The table on the left of **Figure 10** provides space for specifying $\mathbf{L}$, with the table on the right of **Figure 10** providing space for specifying $\mathbf{M}$. In each case enough rows/columns are provided to allow

for an identity matrix of suitable dimensions (easily specified using the `Identity matrix` button). However, it is not necessary to use all the rows for any particular contrast (although all columns must be filled).

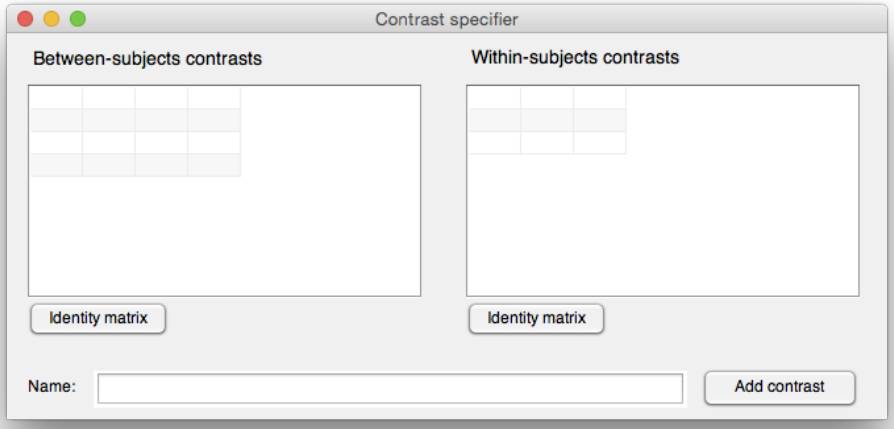


Figure 10 – The interface for specifying contrasts in the general linear hypothesis test $\mathbf{LBM}' = 0$

In order to specify the contrast for the `Main effect of Age` we need to first think about what this hypothesis test actually means. In the context of our repeated measures model this is the effect of the `Age` factor (i.e. older - younger) averaged over both `Diagnosis` and `Condition`. This can therefore be specified using $\mathbf{L} = \begin{bmatrix} 0.5 & 0.5 & -0.5 & -0.5 \end{bmatrix}$ and $\mathbf{M} = \begin{bmatrix} 0.33 & 0.33 & 0.33 \end{bmatrix}$. In fact, the fractional values are unnecessary, with the same test provided using $\mathbf{L} = \begin{bmatrix} 1 & 1 & -1 & -1 \end{bmatrix}$ and $\mathbf{M} = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix}$. This makes for a much easier specification, as shown in **Figure 11**. Referring back to the design visualisation can also make for an easier specification of weights to columns by using the column labels. Note, however, that because the design visualisation represents $\mathbf{Y} = \mathbf{X}$ and the contrast specifier represents $\mathbf{LBM}$, the different portions of the design are reversed. This is easier to see in the current example as the four columns on the *left* of the contrast specifier map onto the four columns of $\mathbf{X}$ on the *right* of the design visualisation. Similarly, the three columns on the *right* of the contrast specifier map onto the three columns of $\mathbf{Y}$ on the *left* of the design visualisation. This is shown visually in **Figure 12**.

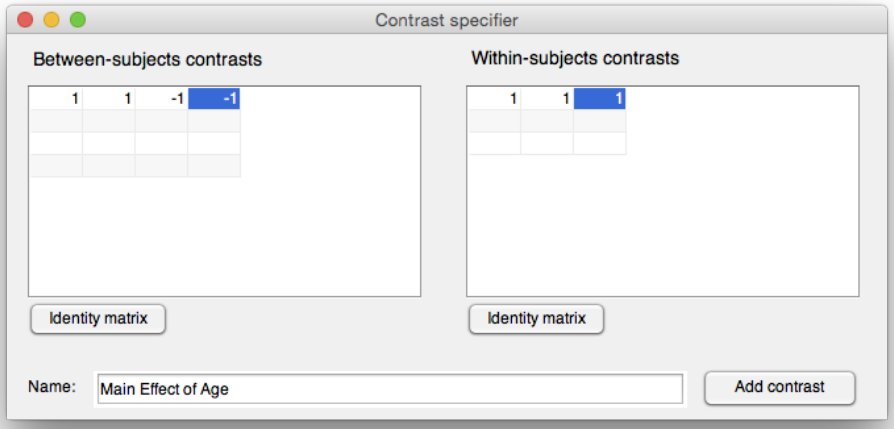


Figure 11 – The `Main effect of Age` contrast

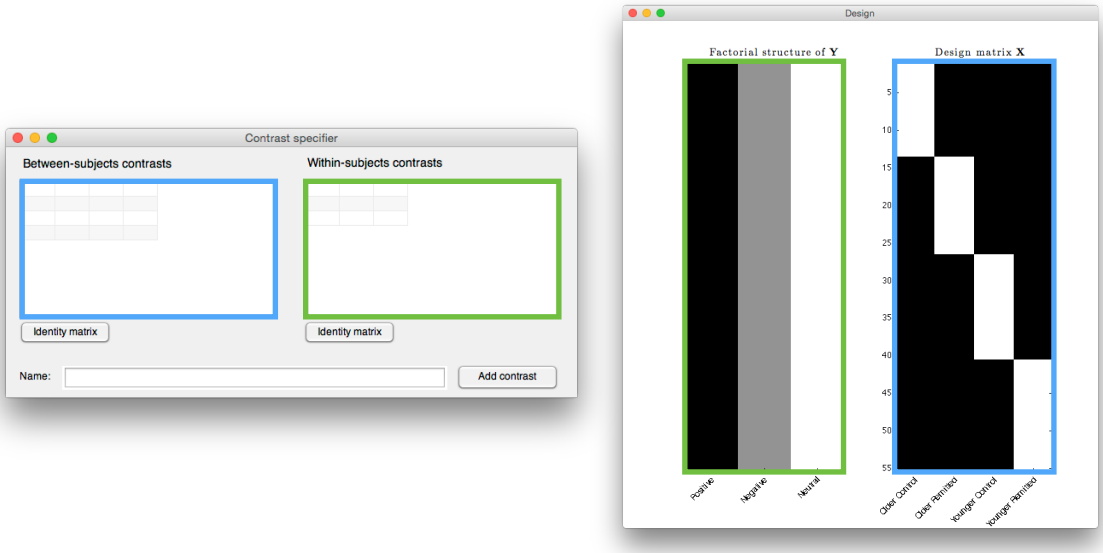


Figure 12 – Demonstration of how the contrast specification and the model visualisation are reversed. Here the *between-subject* contrast maps onto the columns of the design matrix $\mathbf{X}$ (highlighted in *blue*), whereas the *within-subject* contrast maps onto the columns of the outcome matrix $\mathbf{Y}$ (highlighted in *green*). This is done to maintain consistency with the differing orders of the model ($\mathbf{Y} = \mathbf{XB} + \mathbf{E}$) and the hypothesis test ($\mathbf{LBM}'$).

Pressing the `Add contrast` button will append the contrast to the list. Continuing in this fashion (or simply pressing the `Generate standard ANOVA contrasts` button) will provide the list of tests shown in **Figure 13**.

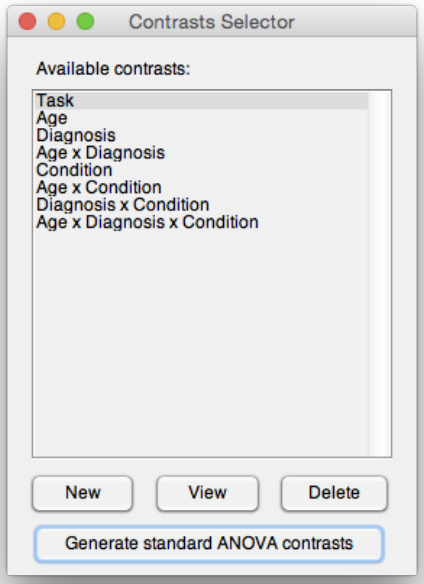


Figure 13 – The full set of contrasts for the ANOVA tests in the example model

Closing this window will update the main model specification window with the number of contrasts. Here the multivariate tests statistic you wish to use can also be selected from the drop-down menu. A test can also be performed, using the `Exact test` button, to tell you whether you need to worry about choosing a test statistic. This is based on seeing if all contrasts provide $\text{rank}(\text{SSCP}_H) = 1$. If they do then all the tests statistics will provide identical F values (as all the SSCP_H matrices should be 1×1). In which case the statistic used does not matter. Generally in these cases Wilks' Λ will be fastest.

1.4 Multiple comparison correction

A consistent problem with mass univariate approaches to modelling neuroimaging data is that they engender a very large multiple comparison problem. The mass multivariate approach is no different in this respect. In MRM a number of options are available for thresholding results in order to control for this issue. These are all available via the drop down menus in the `Inference` section of the model specification window. In this section I will detail the various options available via the `Thresholding` menu.

1.4.1 Thresholding: None

The first thresholding option is to perform no thresholding at all. Here only the test statistics and p-values are calculated, with no correction made to the p-values and no thresholding performed on any of the images. In terms of options it is possible to calculate these p-values either by permutation methods, or using the p-values given by the F-approximations to the multivariate test statistics. These

options can be selected using the `P-value calculation` drop-down menu. When using permutation approaches it is possible to specify the number of permutations performed in the `No. permutations` box, defaulting to 5,000.

1.4.2 Thresholding: Uncorrected

The second thresholding option is to use an uncorrected p-value threshold. Here the test statistics and p-values are calculated, with both thresholded and un-thresholded statistical maps provided. The thresholding is performed on a voxel basis, and corresponds to only returning statistical values when $p <$ threshold. This threshold can be set using the `Uncorrected P threshold` box, defaulting to 0.001. As with the no thresholding approach, the p-values can be calculated using either permutation or approximate methods.

1.4.3 Thresholding: Voxel

The third thresholding option is to use some form of voxel-level p-value correction. This p-value correction comes in two flavours, either using the false discovery rate (FDR) correction, or by providing a familywise error (FWE) correction via permutation methods. These can be selected from the `Correction method` menu, and are similar to other neuroimaging approaches, though FWE correction is more usually applied by appealing to Gaussian random field theory. Permutation approaches, though more computationally burdensome, provide a more sensitive analogue to this correction, with fewer assumptions about the nature of the data. Like the uncorrected approach, the thresholding is performed on a voxel basis, but corresponds to only returning statistical values when $p_{\text{corr}} <$ threshold. Where p_{corr} could either be FDR-based (p_{FDR}) or FWE-based (p_{FWE}). In both cases the threshold defaults to 0.05, but can be changed via the `Corrected P threshold` box. In addition, the uncorrected p-values that are plugged into the correction method can be calculated either approximately or via permutation. If approximate p-values are used then only FDR correction is available. If permutation p-values are used then both FDR and FWE are available.

1.4.4 Thresholding: Cluster

The final thresholding option is based on tests performed at the cluster level. Here the approach involves defining an initial cluster-forming threshold to break the image into clusters, defining which voxels belong to which clusters using a 26-adjacent scheme (i.e. faces, corners, and edges), and finally defining some metric of each cluster. These metrics are then subjected to a statistical test to determine a p-value for each cluster. In MRM these metrics can either be cluster size (the number of voxels in a cluster) or cluster mass (the sum of the test statistics within the cluster), and can be change via the options window available from the MRM menu. Because the null distribution of these metrics is relatively intractable only permutation approaches allow for a suitable designation of p-values to both measures of cluster size and cluster mass. As such, permutation approaches are the *only* option for cluster statistics in MRM. The only options available when using cluster statistics are the cluster-forming threshold, which can be changed using the `Cluster-forming P` box, the threshold on the cluster statistics, which can be changed using the `Cluster P` box, and the

number of permutations, which again can be changed using the `No. permutations` box.

1.4.5 Current example

For the current data we choose to use voxel-level permutation tests to provide a FWE correction, thresholding the images at $p_{\text{FWE}} < 0.05$. We leave the number of permutations at the default 5,000. Generally speaking, the more permutations the better, however, 5,000 should be enough to get a good sense of the results. Indeed, if this were only an initial look at the modelling strategy we may choose to instead use non-permutation methods in the interest of speed, turning to permutation approaches only once we are satisfied.

1.5 Other options

The only other options we need to complete are found in the `Options` section of the model specification window. Here we specify both the output directory and the location of any mask we wish to use. If the output directory does not exist then MRM will create it for you. In terms of masking, this options allows the restriction of inference to only certain regions of the brain, helping to reducing the burden of the multiple comparison correction. In doing so it is important that the regions are pre-hypothesised, and not selected on the basis of finding results that may be of interest but do not survive multiple comparison correction. Any mask provided will be binarised and resliced to match the dimensions of the data. Once this information is complete we can either choose to save the model specification (using the `Save` button at the bottom of the window to create a *.mat file that can be loaded at a later time) or begin the estimation procedure by pressing the `Estimate` button. In the current example there is no mask and so we only specify the output directory and press `Estimate`.

1.6 Output

Progress of the parameter estimation and contrast estimation can be viewed in the main MATLAB console window. Though parameter estimation is fast, the use of permutation approaches for the contrasts will make the analysis process much slower. At present contrasts are permuted in series rather than parallel, meaning the permutations for one contrast must finish before the next can start. In general any contrast that simplifies to univariate form will be reasonably quick (around 10 minutes for the 5,000 permutes - though your milage may vary). The multivariate contrasts, however, are much slower. In general it is best to leave the permutations running over night.

Once the estimation procedure has finished there will be a number of files in the output directory. At the top level there should be the following file types

- `Design.jpg` - a copy of the design visualisation
- `MRM_Covar_i_j.nii` - the image of estimates for the ith row and jth column of the variance-covariance matrix Σ

- `MRM_PE_i_j.nii` - the image of parameter estimates for the ith row and jth column of the parameter matrix $\mathbf{B}$
- `MRM.mat` - file containing all the model details. This can be loaded into the model specification window to change any of the model estimation parameters
- `Orthog.jpg` - a copy of the design orthogonality visualisation

There will also be a folder for the contrasts named either `Contrasts` or `PermutationContrasts` depending on the option that was selected. In the current example there is a folder named `PermutationContrasts` containing subfolders for each of the contrast estimated (`Task`, `Age`, `Diagnosis`, `Age_x_Diagnosis` etc.). Inside these folders will be the results of the contrasts. Depending on the options chosen the contents of these folders will differ. Hopefully all the files are named sensibly enough that their contents can be discerned. For the current example the folders contain (with * designating the name of the contrast)

- `MRM_*_refF.nii` - the original image of F-statistics for the contrast. This is the reference image used for counting the number of times the statistic under permutation exceeds the reference value at each voxel
- `MRM_*_refP_UC.nii` - the image of uncorrected (non-permutation) p-values for the reference F image
- `MRM_*_1_minus_refP_UC.nii` - the image of uncorrected $1-p$ values. This is provided to make visualisation easier as larger values equate to smaller p-values
- `MRM_*_permutedP_UC.nii` - the image of uncorrected p-values from the permutations. The values in this image relate to the number of times the reshuffled statistic was greater than, or equal to, the value from the same voxel in the reference F image. These are divided by the number of permutations to provide the p-values. Generally speaking, this image should look very similar to the `MRM_*_refP_UC.nii` image
- `MRM_*_1_minus_permutedP_UC.nii` - the $1-p$ equivalent of the `MRM_*_permutedP_UC.nii` image
- `MRM_*_permutedP_FWER.nii` - the image of FWE adjusted p-values. Here the values relate to the number of times the *largest* reshuffled statistic in the image exceeded the reference F-value at a particular voxel
- `MRM_*_1_minus_permutedP_FWER.nii` - the $1-p$ equivalent of the `MRM_*_permutedP_FWER.nii` image
- `MRM_*_F_FWER_thresholded.nii` - the thresholded version of the `MRM_*_refF.nii` image, where any value with $p_{\text{FWE}} \geq 0.05$ is set to NaN. This can be used to visualise the results in any external viewer program by overlaying on top of a template image
- `MRM_*_Results.txt` - a text file containing the list of maxima that passed the given threshold for significance. In our current example this is the list of maxima where $p_{\text{FWE}} < 0.05$. The separator here is the `|` symbol, which needs specifying for import into other programs (e.g. Excel)

- `nullDist.jpg` - a histogram of the null distribution of the maximum F in the image used to calculate the FWE adjusted p-values. Here the given threshold (e.g. 0.05) is marked, as is the largest value found in the `MRM_*_refF.nii` image. An example, for the main effect of diagnosis, is given in **Figure 14**

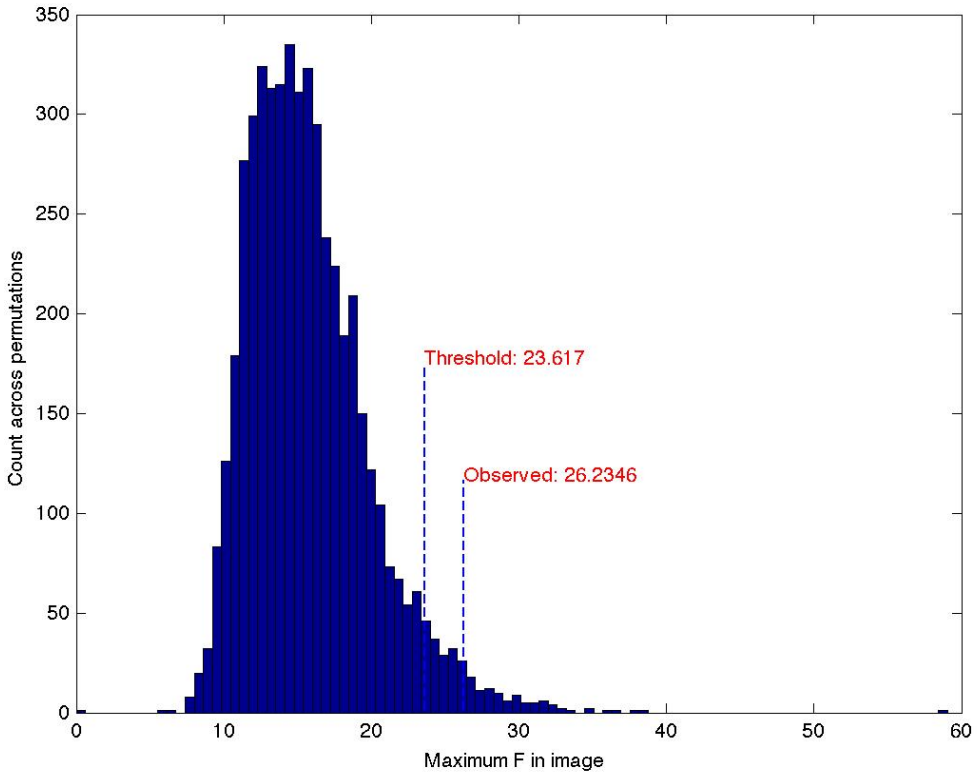


Figure 14 – Example null distribution of the maximum F-value in the image across reshuffles. The 5% threshold is marked, as is the largest F found in the original image. This distribution defines the FWE-corrected p-values

1.7 Post-estimation tools

Though investigation of our results could be performed outside of MRM using the files detailed above, there are a number of useful facilities built directly in to MRM. Returning to the MRM launcher window in **Figure 1** we can press the `Post-estimation tools button` and select the `MRM.mat` file from the output directory when prompted. This will launch the interface shown in **Figure 15**

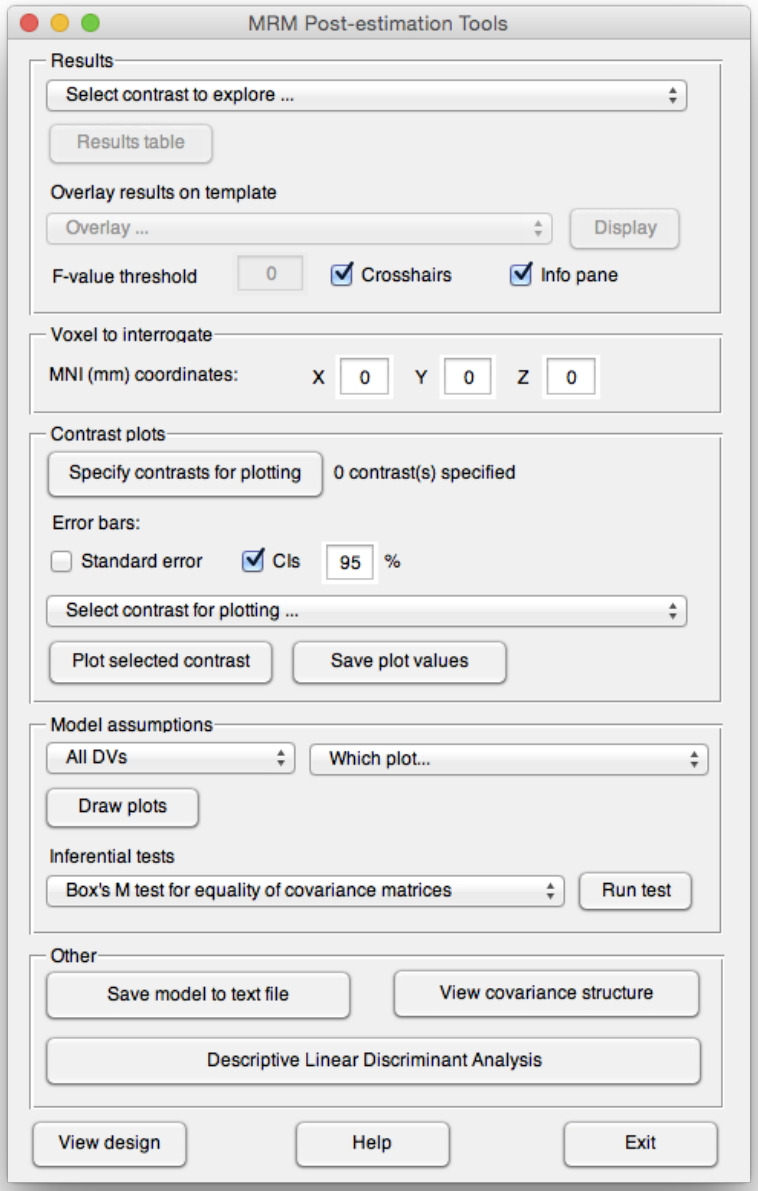
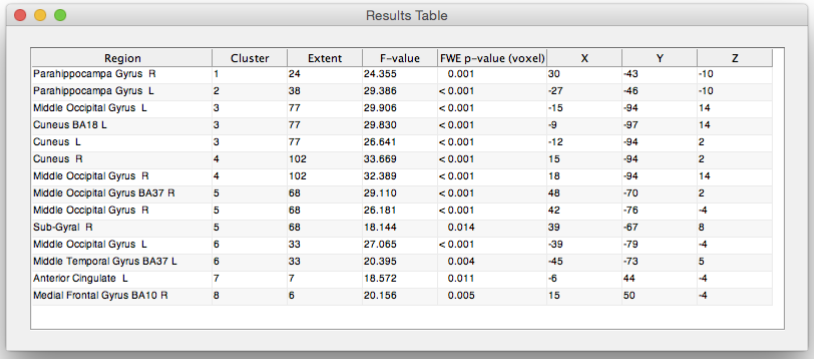


Figure 15 – The interface for the MRM Post-estimation Tools

1.7.1 Exploring results

Starting in the `Results` section at the top of the window, we can select any one of the estimated contrasts from the `Select contrast to explore ...` drop down menu. For this example we select the `Condition` contrast. This will make the `Results table` button active allowing us to display the `MRM_Condition_Results.txt` file in an interactive table, as shown in **Figure 16**



Region	Cluster	Extent	F-value	FWE p-value (voxel)	X	Y	Z
Parahippocampa Gyrus R	1	24	24.355	0.001	30	-43	-10
Parahippocampa Gyrus L	2	38	29.386	< 0.001	-27	-46	-10
Middle Occipital Gyrus L	3	77	29.906	< 0.001	-15	-94	14
Cuneus BA18 L	3	77	29.830	< 0.001	-9	-97	14
Cuneus L	3	77	26.641	< 0.001	-12	-94	2
Cuneus R	4	102	33.669	< 0.001	15	-94	2
Middle Occipital Gyrus R	4	102	32.389	< 0.001	18	-94	14
Middle Occipital Gyrus BA37 R	5	68	29.110	< 0.001	48	-70	2
Middle Occipital Gyrus R	5	68	26.181	< 0.001	42	-76	-4
Sub-Gyral R	5	68	18.144	0.014	39	-67	8
Middle Occipital Gyrus L	6	33	27.065	< 0.001	-39	-79	-4
Middle Temporal Gyrus BA37 L	6	33	20.395	0.004	-45	-73	5
Anterior Cingulate L	7	7	18.572	0.011	-6	44	-4
Medial Frontal Gyrus BA10 R	8	6	20.156	0.005	15	50	-4

Figure 16 – Displaying a results table

This table is interactive, and will update the coordinates in the Post-estimation Tools window as particular maxima are selected. Below the `Results table` button is another drop-down menu for selecting which results to display overlayed on a template. We have a choice of either the thresholded results (the `MRM_Conditon_F_FWER_thresholded.nii` image) or the unthresholded results (the `MRM_Condition_refF.nii` image). If we chose the unthresholded results we can supply our own threshold in the `F-value threshold` box. For this example we select the thresholded results and press the `Display` button. This will launch the viewer window shown in **Figure 17**

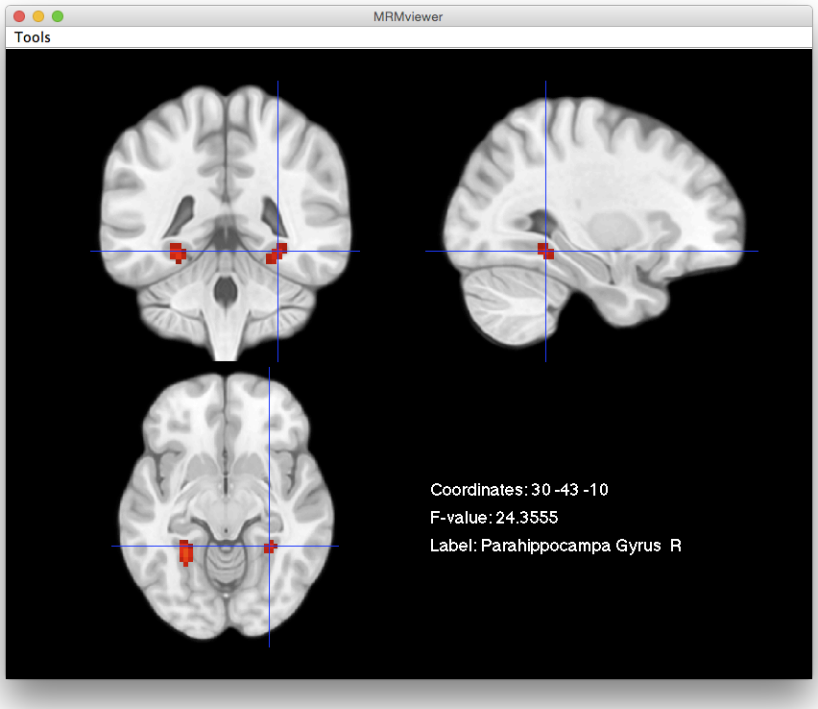


Figure 17 – The image viewer window

This viewer window is interactive (you can click around in the image). Coordinates in MNI space are provided, alongside the statistic value of the voxel and the label from the currently chosen labelling scheme. There are also functions (via the `Tools` menu) to go to the nearest and global maximum, as well as saving the image as a *.jpg file. Both the template image used and the labelling scheme can be changed via the `Options` button on the MRM launcher window. Note, however, that the labels provided in the results table are those taken from the `MRM_*_Results.txt` file, whereas those in the viewer are taken from the currently chosen labelling scheme. If the labelling scheme is changed between estimating the contrast and viewing the results then the labels wont match. Again, all the windows are wired together such that clicking through the results in the table will update the position of the crosshairs in the viewer, and going to the nearest maximum in the viewer will update the highlighted row in the table. MNI coordinates can also be entered manually in the Post-estimation Tools window to update the viewer. This can be done by typing coordinates into the `MNI (mm) coordinates` boxes, or using the up and down arrow keys to move the crosshair through the selected dimension of the image.

1.7.2 Plots of the parameter estimates

More detailed exploration of the results at individual voxels can be achieved by plotting linear combinations of the parameter estimates. This is achieved by supplying contrasts. For users of SPM this approach will be familiar. As an example, we currently have the `Condition` contrast selected, and will therefore be interest in a plot showing us the means of the different conditions, but averaged over the different groups. This can be achieved by supplying $\mathbf{L} = \begin{bmatrix} 0.25 & 0.25 & 0.25 & 0.25 \end{bmatrix}$ and $\mathbf{M} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$. Here, the between-subject contrast $\mathbf{L}$ averages over the groups (the rows of $\mathbf{B}$), with the within-subject contrast $\mathbf{M}$ simply a $t \times t$ identity matrix. Of note is the fact that fractional values *are* necessary here in order to display accurate values in the plot. Showing this explicitly

$$\begin{aligned}
\mathbf{LBM}' &= \begin{bmatrix} 0.25 & 0.25 & 0.25 & 0.25 \end{bmatrix} \begin{bmatrix} \mu_{111} & \mu_{112} & \mu_{113} \\ \mu_{121} & \mu_{122} & \mu_{123} \\ \mu_{211} & \mu_{212} & \mu_{213} \\ \mu_{221} & \mu_{222} & \mu_{223} \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \\
&= \begin{bmatrix} \mu_{..1} & \mu_{..2} & \mu_{..3} \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \\
&= \begin{bmatrix} \mu_{..1} & \mu_{..2} & \mu_{..3} \end{bmatrix}
\end{aligned}$$

Finding the appropriate standard errors for these estimates can be achieved by noting that the variance of the contrast $\hat{\psi} = \mathbf{l}\hat{\mathbf{B}}\mathbf{m}'$, where both $\mathbf{l}$ and $\mathbf{c}$ are single-row, is given by

$$\mathrm{Var}(\hat{\psi}) = (\mathbf{m}'\boldsymbol{\Sigma}\mathbf{m})[\mathbf{l}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{l}']$$

Because in our example $\mathbf{L}$ is already single-row all we need do is calculate the above quantity using the individual rows of $\mathbf{M}$ and our unbiased estimate of $\boldsymbol{\Sigma}$. Taking square roots leads to an estimate of the standard error of the quantity given by $\mathbf{l}\hat{\mathbf{B}}\mathbf{m}'$, from which we can calculate asymptotic 95% confidence intervals. Such a procedure can be easily generalised to cases where both $\mathbf{L}$ and $\mathbf{M}$ contain multiple rows.

In order to create plots of the parameter estimates we select the `Specify contrasts for plotting` button. This will open the interface in **Figure 18**, very similar to the interface seen earlier. Here the list of available plotting contrasts will be shown. To specify a new contrast we press the `New` button to open the interface in **Figure 19**.

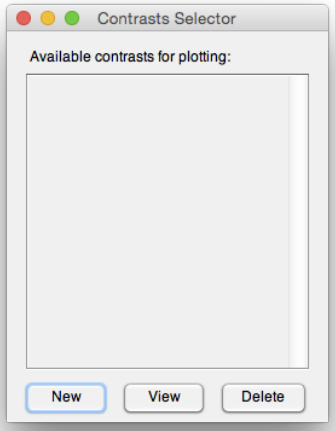


Figure 18 – The list of contrasts available for plotting

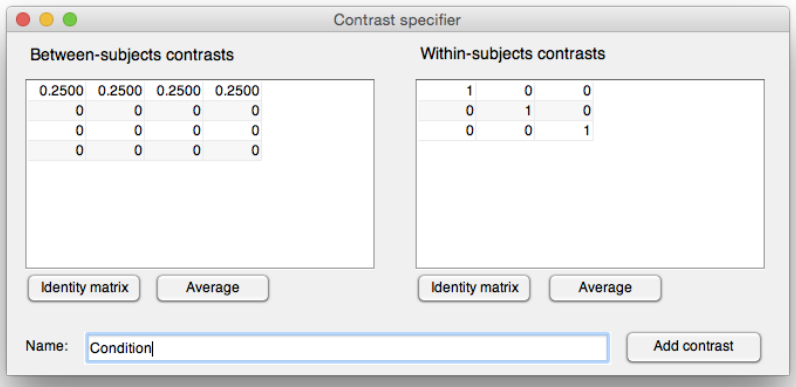


Figure 19 – The interface for specifying plotting contrasts. Here the contrast for `Condition` is shown

Again, this interface should seem familiar. However, a new convenience function is available via the `Average` button, providing appropriate weights for averaging across the columns of either **L** or **M**. In our example we wish to average across the between-subject groupings, but maintain the different within-subject conditions. This is easily done by pressing the `Average` button below the `Between-subject contrasts` table, and pressing the `Identity matrix` button below the `Within-subject contrasts` table. This leads to the contrast shown in **Figure 19** (note that the rows

containing all zeros are unnecessary, and are simply a by-product of calculating the averages. Any row containing all zeros is removed when the contrast is added). Once we have named the contrast we press the `Add contrast` button to update the list in **Figure 18**. At this point we could continue adding contrasts, but for now we will simply close the contrast list window.

Returning to the Post-estimation Tools window, the contrasts we have specified for plotting can now be selected from the `Select contrast for plotting ...` drop-down menu. Selecting `Condition` from this list and pressing the `Plot selected contrast` button will produce the graph in **Figure 20**. The confidence level can be adjusted using the `CIs` box (default to 95%). This plot window is also linked to the other windows so that interacting with the image viewer will update the plot, as will selecting different results in the results table, or supplying different coordinates in the main Post-estimation Tools window. The values used to draw the plot can also be saved to a text file using the `Save plot values` button. These can then be imported into a different program to create your own plots.

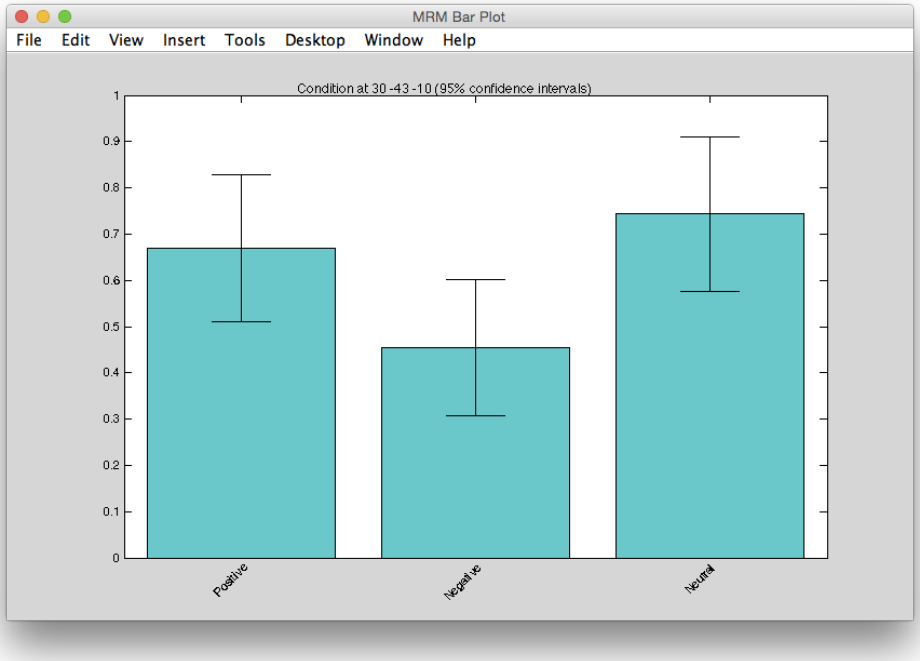


Figure 20 – An example of a plot of the parameter estimates

1.7.3 Checking the model assumptions

Facilities are also available in MRM to check the parametric assumptions of the model. For the multivariate GLM it is assumed that each row of data in $\mathbf{Y}$ is drawn from a multivariate normal distribution, with a mean vector dependent on the values for that row in $\mathbf{X}$, and a variance-covariance matrix $\mathbf{\Sigma}$. Because this assumption relies on the values of $\mathbf{X}$, it can be more usefully specified in terms of the model residuals, such that for the ith row

$$\mathbf{E}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{\Sigma})$$

where $\mathbf{0}$ is a vector of zeros, and $\sim$ designates "distributed as". Implicit in this statement are two main assumptions, namely that the errors should appear to conform to a multivariate normal distribution, and that the covariance matrix should be the same for all groups (*covariance homogeneity*). A number of plots and inferential tests are available in MRM in order to assess these assumptions.

In the `Model assumptions` section of the Post-estimation Tools window several plots are available

- `Histogram of residuals` - used for assessing the residual distribution
- `Normal QQ plot of residuals` - used for assessing the residual distribution by seeing how well the points lie on the marked diagonal line
- `Fitted values against residuals plot` - used for assessing homogeneity of variance by seeing whether approximately equal numbers of points are seen above and below zero across the fitted values
- `Box and jittered scatter plots of the data` - used for assessing the symmetry of the distribution and indicating outiers
- `Scatter plots of DV pairs in each group` - used for assessing covariance homogeneity across groups by showing scatter plots of DV pairs with the contour curves of their implied distribution shown. Here the contours should be of a similar size and pointing in similar directions

In each of these cases we can select whether to show the plots for all the DVs, or for a particular DV. When using all DVs for the distributional assumptions the plots are created for each column of $\mathbf{E}$, as well as a single linear combination of the columns of $\mathbf{E}$ (the sum). This should generally be enough to assess multivariate normality. Inferential tests can also be used alongside the plots. From the `Inferential tests` drop-down menu we can select either Box's M-test for covariance homogeneity, or Levene's tests of variance homogeneity. The former is of most use in the multivariate case, with the latter providing more utility when exploring individual DVs. In both instances an $\alpha = 0.001$ is recommended. For the current data at a particular voxel of interest (30 -43 -10) Box's test given $M = 18.502$, with the F approximation providing $p = 0.558$. This suggests no problems with unequal covariance matrices. In general it is recommended to use these inferential tests with a certain amount of caution, and in conjunction with the visual depictions of the assumptions given by the various plots. For permutation approaches some of these assumptions are less critical. Indeed, the assumptions of multivariate normality is unnecessary, though a symmetric distribution is still necessary for sign-flipping to be a legitimate approach. The assumption of variance-covariance homogeneity, however, is still in effect as the multivariate tests statistics themselves are predicated on assuming that a pooled covariance structure can be used in the calculations.

1.7.4 Exporting results

In many situations it may be useful to get the results for a particular voxel out of MRM. To do we can press the `Save model to text file` button in the `Other` section of the MRM Post-estimation Tools window. After selecting the output directory three files will be written. For our voxel of interest (30 -43 -10) these files are

- PredictedValues_30_-43_-10.txt
- RawData_30_-43_-10.txt
- Residuals_30_-43_-10.txt

The first contains the predicted values of the model, given by $\mathbf{X}\hat{\mathbf{B}}$, the second contains the raw data for the voxel, and the last contains the residuals of the model, given by $\hat{\mathbf{E}} = \mathbf{Y} - \mathbf{X}\hat{\mathbf{B}}$.

2 Analysing different modalities

Beyond repeated measurement designs, the multivariate GLM framework in MRM is also useful for investigations where multiple modalities of imaging data are collected to inform on differences between groups of interest. Traditionally these modalities would be analysed in isolation, however, the MANOVA tools in MRM allow the specification of a simple multivariate model that accommodates all modalities. This can then be extended through the use of descriptive linear discriminant analysis (*d*LDA) to assess the degree to which the individual modalities are contributing to the separation of the groups of interest.

2.1 The data

For the second example we will use a subset of the data described in **Section 1.1**. Focussing on just the younger adults during the `Negative` picture condition, we are interested in seeing whether there are differences in brain function between the controls and previously depressed subjects that relate to differences in grey matter volume. To do so we will fit a multimodal model using the MANOVA functions built into MRM. This will equate to a combined fMRI and voxel-based morphometry (VBM) analysis. In this example the functional data are simply the parameter estimated from the 1st-Level modelling that relate to the `Negative` picture condition. For the structural data we produce normalised grey matter maps using the SPM DARTEL tool (see `http://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf`).

2.1.1 Proportional scaling

One particular issue with analysing VBM data is the accommodation of different head sizes. Though such an issue is rather specific to structural data, I cover it here because it highlights the fact that processing steps specific to a particular modality *must* be performed on the data before modelling it in MRM. Though in SPM the option exists to proportionally scale the data, no such option is available in MRM. As such we must scale the normalised grey matter images produced by DARTEL ourselves. This is preferable to entering e.g. total intracranial volume as a covariate in the analysis as in the multivariate framework any covariate will influence the parameter values for all modalities. This could therefore have some unforeseen consequences for the parameters associated with the functional data. For the current example we use the SPM Image Calculator to scale each image using e.g. `i1 ./ totalIntercranVol`, where `totalIntracranVol` is a variable containing the total intracranial volume for that particular subject.

2.1.2 Data dimensions

Another issue when working with multiple modalities is that the dimensions of the images will likely differ. In the current example the images of parameter estimates from the functional scans are $53 \times 63 \times 53$, whereas the grey matter images produced by DARTEL are $121 \times 145 \times 121$. In order for the multivariate approach to work we need each voxel in each modality to line-up. As such we need all the images to be the same dimensions. Although the preprocessing steps of each modality could be altered to try and produce images of the same dimension, in many cases it may be easier to

stick to standard preprocessing pipelines and reslice (resample) the images at the end. This naturally leads to the question of which way round to perform the resampling? It may initially seem like the best approach is to resample the lower resolution image to size of the higher resolution image. Using an approach such as nearest-neighbour interpolation means all the original values in the image are retained and are essentially just duplicated. However, from a computational perspective, if one wished to use permutation inference with multivariate tests statistics on images of dimension $121 \times 145 \times 121$ it will take a very long time. This would suggest that resampling the higher resolution image to size of the lower resolution image is more advantageous. There is very little data available to suggest which way round is best, and ultimately will have to be based on your own personal preferences. My own limited tests of the different approaches suggest little difference in terms of the over all pattern of findings, but again your mileage may vary. For the purposes of this tutorial we choose to reduce the computational burden and go with resampling the structural images to the same dimensions as the functional images. This can be done using the `spm_reslice` function bundled with MRM.

2.1.3 Masking

As a final step we create a mask to restrict inference to only regions of grey matter. We do this for two reasons. Firstly, in the images produced by DARTEL not all values outside of the grey matter are 0 or NaN. As such, these values wont be automatically removed from the analysis. This will slow the analysis down, and may cause computational issues due to precision when working with matrices containing very small numbers. Secondly, we are interested in regions of crossover between the structural and functional findings. As such it would seem sensible to only analyses those voxels where data exists in both modalities. In the current example we create the mask using the SPM Image Calculator to average all the scaled and resliced DARTEL grey matter maps together, and then binarise the resulting image by selecting only those voxels whose intensity is > 0.2. This creates the mask shown in **Figure 21**

Figure 21 – The analysis mask used for the multimodal model. Here the structural images have been resliced to the dimensions of the functional images.

2.2 Specifying the model

To specify a multimodal model click the `MANOVA` button on the MRM launcher window. This will launch the model specification interface shown in **Figure 22**. This window is identical to the repeated-measures model specification window except that *within-subject factors* has now been changed to *DVs*. Indeed, much of the model specification procedure is identical to the repeated-measures case save for the specification of the DVs and the contrasts. As such we will not dwell on the model specification too much, only seeking to highlight the differences with the repeated-measures module. If you skipped over the repeated-measures section now would be a good time to go back and read it through.

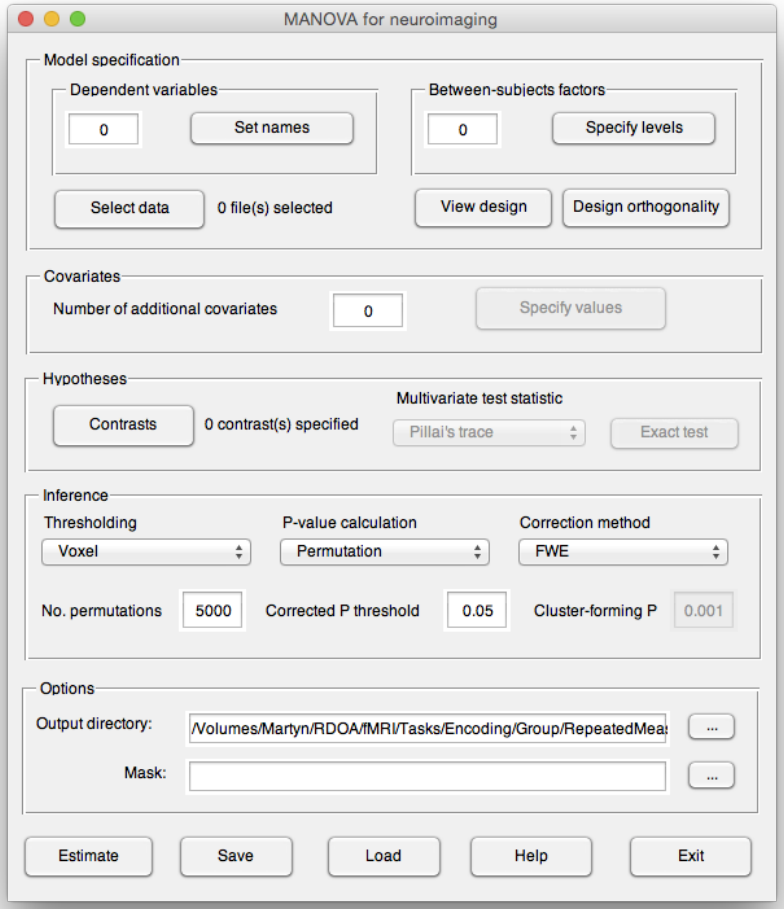


Figure 22 – The MANOVA model specification window

2.2.1 Specifying the DVs

Because in the MANOVA module we are directly specifying the columns of $\mathbf{Y}$ we do not need to specify any form of factorial structure. As such we only need to provide names for the different columns. Changing the `Dependent variables` box from 0 to 2 and clicking on `Set names` opens the interface shown in **Figure 23**. For the current model we enter `VBM` and `Functional` as names of the modalities.

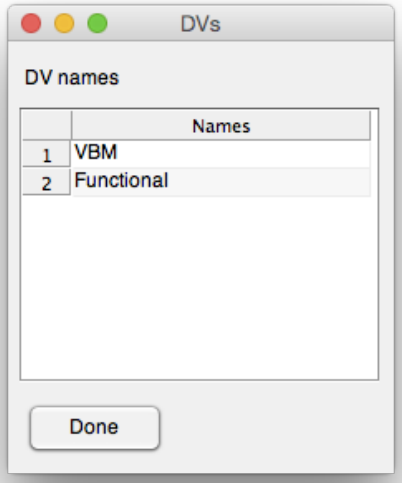


Figure 23 – The DV naming window

Specifying the rest of the design structure is identical to specifying a repeated-measures model, leading to the design shown in **Figure 24**

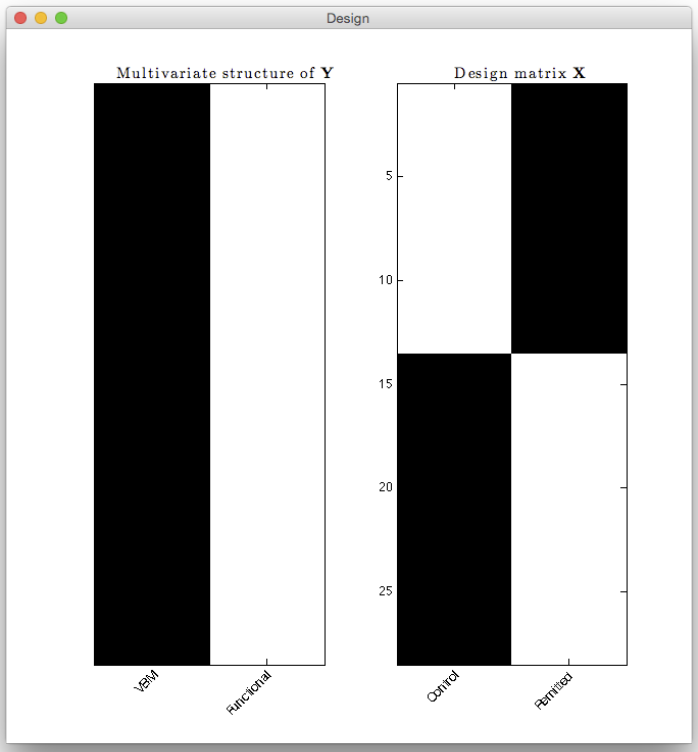


Figure 24 – The multimodal design visualisation

2.2.2 Contrasts in a MANOVA model

It should hopefully be clear by now that there is very little difference between specifying a multimodal model and a repeated-measures model. Indeed, the two approaches are practically identical. Where the core difference lies between the approaches is in the specification of contrasts. As explained in **Section 1.3.1** the multivariate GLM hypothesis testing framework is given by $\mathbf{LBM}' = \mathbf{0}$. When specifying repeated-measures models the forms that $\mathbf{L}$ and $\mathbf{M}$ take can be quite broad. As such, we may used e.g. $\mathbf{M} = [1\ 1\ 1]$ to effectively average over the repeated-measurement conditions. Using an $\mathbf{M}$ matrix of this form in a multimodal context is nonsensical as the modalities are measured on different scales. As such an average of the two is basically meaningless. Indeed, any comparison directly between the modalities would not tell us anything useful. As such, in all MANOVA models the contrasts are given by a variety of $\mathbf{L}$ forms, but always using e.g. $\mathbf{M} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$, the $t \times t$ identity matrix. This means the contrast in $\mathbf{L}$ is performed on the modalities separately, with the information only combined when the multivariate test statistics are calculated, allowing a pooling of the information on a common scale. In MRM any contrast specified in a MANOVA model will automatically provide an identity matrix for $\mathbf{M}$. The only time it would be legitimate to change this would be to provide tests on the modalities individually. As an example, we can specify the contrast for the main effect of group, but for the structural data only, as shown in **Figure 25**

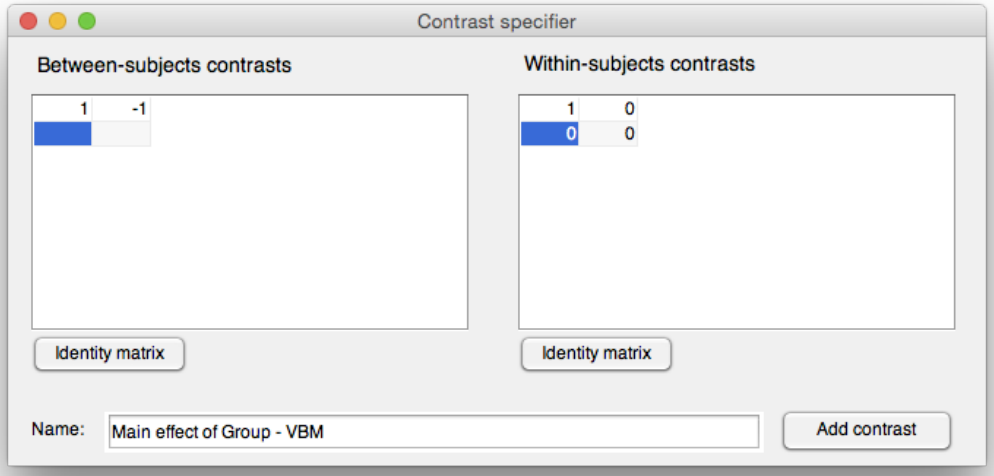


Figure 25 – The contrast for the effect of group in the VBM data alone

2.3 Investigating the results of a MANOVA model

The remainder of the process for estimating a MANOVA model is identical to the repeated-measures case, with a very similar set of output files to those described in **Section 1.6**. Investigation of the results is also similar, however, there are two areas that require some brief discussion. The first is on the issue of plotting the results, and the second is on using a technique known as descriptive linear discriminant analysis

(*d*LDA) to follow-up any significant MANOVA effects.

2.3.1 Plotting contrasts of parameter estimates

As explained in **Section 1.7.2**, more information on the voxel-level results can be gained by plotting certain linear combinations of the parameter estimates. In a MANOVA model this still applies, however, there are two issues worth noting. The first is simply to remember that the modalities are not considered to be commensurate, and therefore plotting linear combinations of them (e.g. $\mathbf{M} = [1\ 1]$) is not an informative thing to do. The second is similar in spirit as the temptation would be to plot some combination of the cell means using e.g. $\mathbf{M} = \left[\begin{smallmatrix} 1 & 0 \\ 0 & 1 \end{smallmatrix}\right]$. However, remembering that the modalities are not on the same scale means it is debatable how useful it is to plot them on the same y-axis. In these cases it is often most useful to plot the modalities separately, e.g. $\mathbf{M} = [1\ 0]$ and $\mathbf{M} = [0\ 1]$.

2.3.2 *d*LDA

A significant MANOVA effect (e.g. the effect of group in the current example) can be interpreted as indicating that our groups significantly differ on some linear combination of the modalities. Of course the natural question is to then ask what that linear combination is. This is where *d*LDA comes in. I wont delve into the technical explanation of how the linear discriminant functions are calculated (see some excellent explanations in Rencher & Christensen, 2012, and Klecka, 1980), rather I will focus on running this analysis in MRM and interpreting the output.

In our current example there is an interesting cluster of results for the main effect of diagnosis in the lingual gyrus. This is shown thresholded liberally in **Figure 26**, but the peak voxel does survive FWE correction, providing a permutation $p_{\text{FWE}} = 0.043$ after 5,000 reshuffles. Making sure the peak is selected, clicking on the `Descriptive Linear Discriminant Analysis` button at the bottom of the Post-estimation Tools window will launch the interface in **Figure 27**

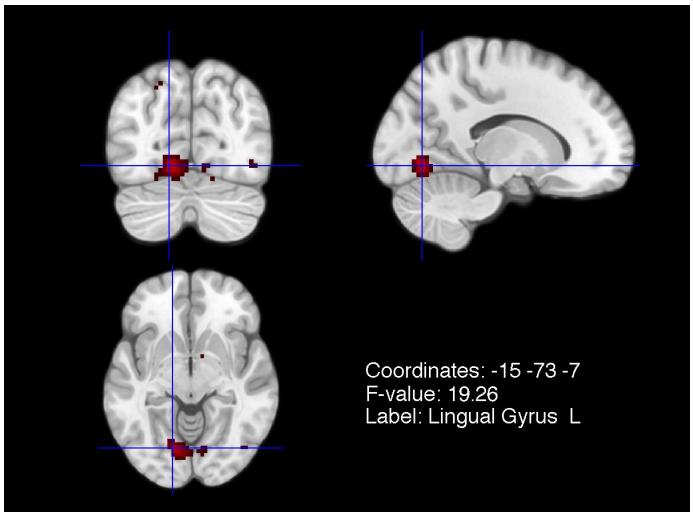


Figure 26 – The multivariare main effect of diagnosis in the lingual gyrus

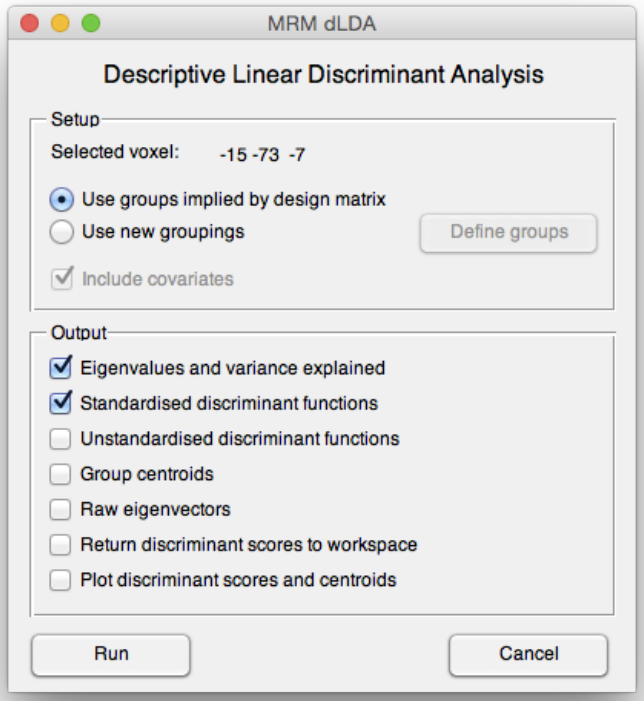


Figure 27 – The dLDA interface

There are a fair few options that can be selected here. The first is whether to calculate the discriminant functions using all the groupings in the design matrix, or whether to redefine the groups to be used. This would be useful if, for example, there were two between-subject grouping variables but you only wished to follow-up an effect of one group (perhaps only one main effect is significant at the voxel of interest). In order to do so we can select `Use new groupings` and then specify the new group number for each subject. This will effectively create a new design matrix that will be used when performing the *d*LDA. Below this is the option to keep covariates in the design when performing the *d*LDA. If covariates are kept then the SSCP_H and SSCP_E matrices are defined based on the model containing covariates. If group membership is redefined, as indicated above, a careful decision should be made about keeping or excluding covariates.

In terms of the `Output` the two options selected by default are the minimum necessary in order to interpret the *d*LDA results. Because the different modalities are on different scales the `Standardised discriminant functions` are the most readily interpretable. It is possible to also return the `Unstandardised discriminant functions` and the `Raw eigenvectors` if desired (the standardised functions are calculated from the unstandardised functions, which in turn are calculated from the eigenvectors). The `Group centroids` can also be returned. These can be interpreted as a form of multidimensional mean, and are the values that are maximally separated by the linear combination of modalities given by the discriminant functions. This can be seen visually be requesting MRM to `Plot discriminant scores and centroids`, though this is only possible when then number of discriminant functions

is > 1. As a final option the discriminant scores themselves can be returned as a variable in the MATLAB workspace.

For the current example we keep things simple and only return the default output. Pressing `Run` will return the following output into the MATLAB console

```
-----------------------------------------------------------------
Descriptive Linear Discriminant Analysis
-----------------------------------------------------------------

Results for voxel: -15 -73  -7

Eigenvalues and variance explained
---------------------------------
Eigenvalues | Variance (%)
     1.5408 |          100


Standardised discriminant functions
-----------------------------------
           | Function 1
       VBM |  -0.825928
Functional |  -0.850116
```

Figure 28 – The dLDA output

Because for our model $\text{rank}(\text{SSCP}_H) = 1$ only a single discriminant function is returned. As such, 100% of the variance is explained. In general there may be several discriminant functions, however, most of the variance is usually explained by only one or two. In terms of the weights themselves we are generally only interested in the magnitude of their absolute value. If we wished to interpret what the function is telling us then the signs of the weights would be of interest. However, in *descriptive* LDA it is simply the magnitude that tells us about how much each modality is contributing to group separation. What is most intriguing about the weights shown in **Figure 28** is that a near equal magnitude is found for *both* modalities, with the VBM providing an absolute weight of 0.826, and the functional data providing an absolute weight of 0.850. This therefore suggests that at this particular voxel it is a near equal combination of the functional and structural information that provided the greatest separation between the two diagnostic groups.

References

- Klecka, W.R., 1980. Discriminant Analysis. Sage, London.
- Miller, G., Chapman, J., 2001. Misunderstanding analysis of covariance. J. Abnorm. Psychol. 110, 40-48.
- Rencher, A.C., Christensen, W.F., 2012. Methods of Multivariate Analysis, 3rd ed. John Wiley & Sons, New York.