NIX Manual

1. Introduction

The NIX is a toolbox to calculate and present interaction effects in non-parametric datasets. It uses the Matlab implementations of the *nparLD* (http://cran.r-project.org/web/packages/nparLD/index.html) toolbox of R statistics (http://www.r-project.org/). Its results are common *Nii-Files* that contain F-, uncorrected p- and FDR-corrected p-values that any imaging visualization tool can display. As interaction effects can be difficult to understand and interpret the NIX-toolbox comes with a visualization tool, especially developed for the NIX-toolbox.

2. How to use NIX

2.1 Operate NIX step-by-step

1.1. Start *Matlab*

1.2. Change the path to the folder where you have extracted the NIX-Toolbox

1.3. Type *NIX* in the Matlab Command Window and press Enter

1.4. Choose “Repeated non-parametric data” (resume at 2.5) or “Contingency Table” (resume at 3.5) (Fig. 1.4).
(if you are not sure about your data, check chapter 3)

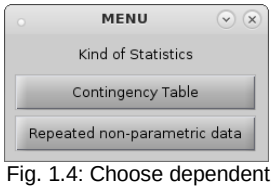


Fig. 1.4: Choose dependent data

2.5. The number of between- and within- factors need to be entered (Fig. 2.5). You have to enter at least one within factor.
Note: The total number of factors is limited to two a maximum of two. Therefore, you can either choose to have no Between- and one Within-factor, one Between- and one Within-factor (Fig.1) or no Between- and two Within-factors.

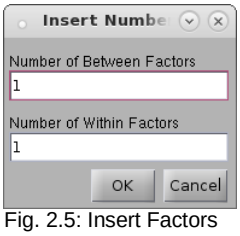


Fig. 2.5: Insert Factors

2.6. Next, enter the factor names and the number of factor levels for the different factors (Fig. 2.6). Each Factor must have at least two levels.
Note: *ImgData* cannot be used as a name for any Between- or Within-factor.

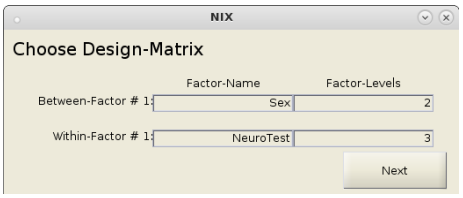
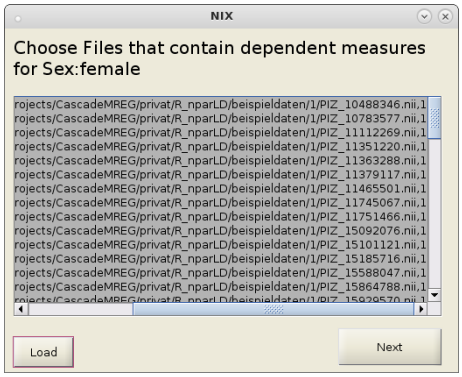


Fig. 2.6: Names and number of levels of the different factors

2.7. Name single factor levels.

2.8. In the next few steps, select the imaging files for the different groups corresponding to the different levels of the between factors specified earlier (Fig. 2.8). Select all files if there is no between-factor.
Note: The file order must match the order of the within data entered in a later step.



The dependent data is entered for each between-factor level separately (Fig. 2.9) but for all within factors and levels (regard column names). You may either enter every value manually or you load an .xls-file.

Note: The .xls-file has to have a first row that contains the names of the columns. No empty cells are allowed anywhere! All dependent data (for the present group) has to be in this one .xls-file.

If you load an .xls-file you will be prompted to choose a selection variable in the file (Fig. 2.9.1). This is handy if you have stored dependent data for more than one group in the file. If you choose a selection variable, another window appears (Fig. 2.9.2) in which you may select the value of the selection variable that corresponds to the group you are loading the data for. If you do not wish to use a selection variable, simply choose "*None → All rows are chosen*" (in that case Fig. 2.9.2 is skipped).

In the next windows (Fig. 2.9.3) select the column names corresponding to the levels of the within factors. (You will receive an error message if the number of rows in the .xls-file and the number of loaded NII-files do not match.)

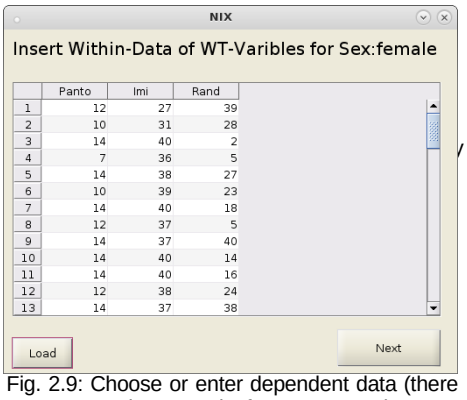
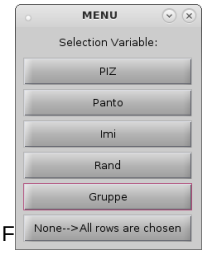


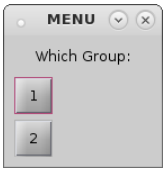
Fig. 2.9: Choose or enter dependent data (there are separate input masks for every group)

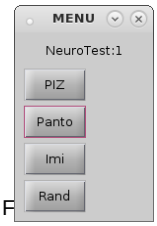
2.9. The next window contains all your entered data (Fig. 2.10).

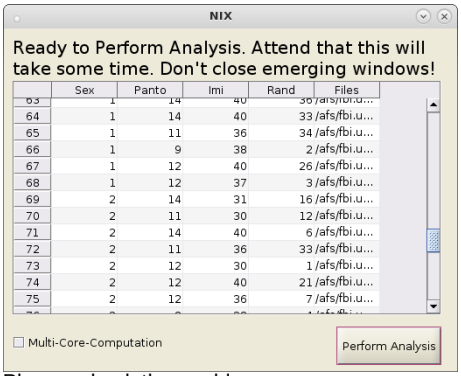
It is strongly recommended that you check whether your dependent data corresponds to the respective imaging file mistakes occur if the imaging data was not selected in the same order as the data listed in the .xls-file (this depends mostly on the naming of the files and that different operating systems tend to sort filenames differently (namely considering or ignoring the capitalization of letters)).

Note: A checkbox at the bottom asks for multiple-CPU calculation. This will only influence the time the calculations will need. If you are unsure leave it unchecked.









Please, check thoroughly.

2.10. This prompt asks for a nominal FDR threshold[1]. That means only voxels with at least the entered amount of subjects for every group (all levels of Between-factors and with/without lesion) are entered in the correction. The value has to be at least 2. All results are always also saved uncorrected.

2.11. You will be asked what kind of statistic test you want to calculate. Most probably you want to choose *ANOVA-Type*.

Note: See chapter 4 for a brief or the original sources[2] for more elaborated descriptions.

2.12. Choose the folder the results should be saved in.

[1] The FDR correction is reasonable because the tests are performed in a voxel-wise fashion. Given the high number of voxels, the α–error inflates resulting in false positive findings. The basic principle of the FDR-correction is that the more values you enter the stricter the statistical threshold gets and, therefore, the higher the effects have to be not to vanish. Unfortunately, there is no perfect way to approach this issue. If you want to include all voxels in the FDR-correction choose "2".

[2] Brunner, E., Domhof, S., & Langer, F. (2002). *Nonparametric Analysis of Longitudinal Data in Factorial Experiments*. New York: Wiley.
Brunner, E., Munzel, U., & Puri, M. L. (1999). Rank-score tests in factorial designs with repeated measures. *Journal of Multivariate Analysis*, 70, 286-317.
http://cran.r-project.org/web/packages/nparLD/index.html

Resume here if you want to analyze contingency tables
(if you are not sure about your data, check chapter 3)

3.5. Choose the number of dimension of your contingency table (at least two; otherwise go to MRIcron).

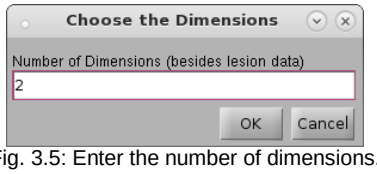


Fig. 3.5: Enter the number of dimensions.

3.6. Choose the names and the levels of your previously chosen factors. You must not name anything *ImgData*.

3.7. Name your factor levels for later identification.

3.8. Enter the *imaging files* for the groups asked in the title.

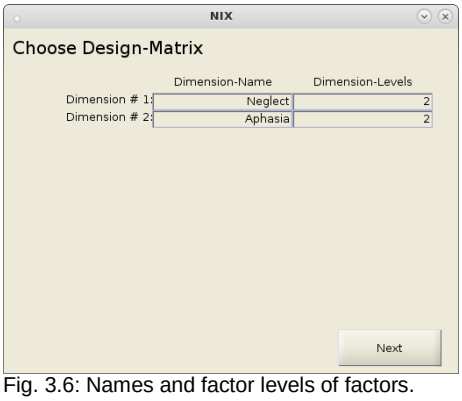


Fig. 3.6: Names and factor levels of factors.

3.9. You get an overview. Check whether that is correct. If not please start over. Continue with *Perform analysis*.

3.10. This prompt asks for a nominal FDR threshold[3]. That means only voxels with at least the entered amount of subjects for every group (all levels of Between-factors and with/without lesion) are entered in the correction. The value has to be at least 2. All results are always also saved uncorrected.

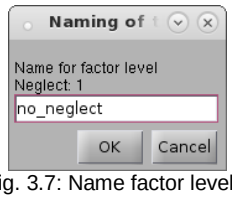


Fig. 3.7: Name factor levels.

3.11. Choose the folder the results should be saved in.

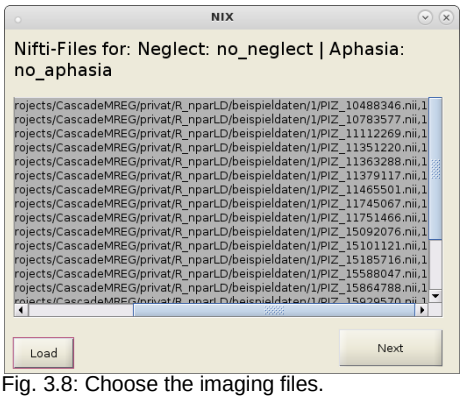


Fig. 3.8: Choose the imaging files.

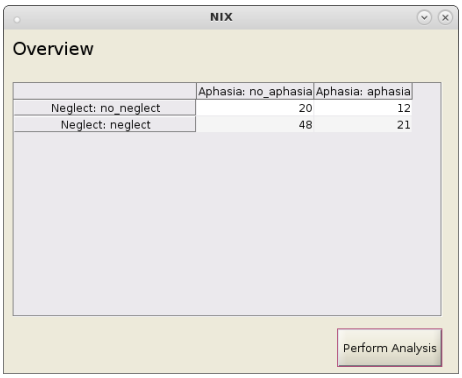


Fig. 3.9: Check the overview of your entered data.

[3] The FDR correction is reasonable because the tests are performed in a voxel-wise fashion. Given the high number of voxels, the α–error inflates resulting in false positive findings. The basic principle of the FDR-correction is that the more values you enter the stricter the statistical threshold gets and, therefore, the higher the effects have to be not to vanish. Unfortunately, there is no perfect way to approach this issue. If you want to include all voxels in the FDR-correction choose “2”.

2.2 Calculation

In this step there is nothing to do but wait. You can observe the Matlab Command Windows to follow the ongoing steps. There is a bar that is graphically filling up.

The computation time strongly depends on very different aspects.

- Speed of your processor and size and speed RAM.
- The amount of processor cores you chose.
- Dimensions/resolution of the loaded imaging data.
- Sample size.
- The Amount of factors.
- Heterogeneity and size of the lesions.

2.3 Results of the NIX-Toolbox

You find the results in the folder you specified (see 2.2.2.13 and 2.2.3.11). For each analysis, there will be a subfolder named after the date on which the calculation was performed. You may move this folder with its content after the calculations have finished, but if you want to use the NIX display tool you must not rename or delete any files stored within the folder.

The date subfolder contains *F-*, *p-*, *and pFDRadj*-Files for every main effect and interaction. All main effect files names consist of the values they contain (*F*, *p*, or *pFDRadj*), an underline and the given effect name (see 2.2.2.5. and 2.2.3.5). All interaction effect file names consist of the values they contain (*F*, *p*, or *pFDRadj*), an underline and all given effect names (see 1.5.) separated by an *X* (i.e. the F-values of the interaction between *group* and *time* are stored in the file *F_groupXtime.nii*).
The effects of the imaging data/lesions are saved in the files with *ImgData* (e.g. *F_ImgData.nii* contains the F-values for the main effect of lesion vs non-lesion; *p_ImgDataXgroup.nii* contains the p-values of the interaction between lesion/non-lesion and the groups).

You will also find files that start with *Diff_PostHoc_for*. They contain score differences, so you can further investigate and understand a significant interaction. The name indicates the post-hoc data that was analyzed (i.e. *Diff_PostHoc_for_Group2__WithinFact2_vs_Within Fact3.nii* analyzed for the second level of the between-factor *Group,* the interaction between lesioned and not-lesioned voxels and the one within-factor *WithinFact* with its second and third level). The formula is calculated for every between level separately and reads as follows:

(WT1value(non-lesioned)) – WT1value(lesioned)) – (WT2value (non-lesioned) – WT2value(lesioned))

Furthermore, you will find two files named NoVar.nii and NoGroupVar.nii. NoVar.nii contains a *1* in every voxel that had no variance between the imaging data (so either no one or every one of the sample had a lesion in this particular voxel). Furthermore, in NoGroupVar.nii a *1* is in every voxel where there was some variance[4] but not enough for an analysis. The nparLD R-package is only calculable if every cell of your design matrix has at least two entries.
Therefore, e.g. if you have three groups, in every of the three groups there have to be at least two subjects with a lesion for this particular voxel and at least two persons without a lesion in this particular voxel to perform an analysis for this particular voxel.

[4] in detail too few variance means: either ((no one) or (only one person) in any group) or ((every one) or (every one but only one) of any group) had a lesion in this particular voxel
i.e. for every voxel the analysis is only performable if there are at least two people in every group who have a lesion in this voxel and two who do not

Thus, if you do not find the results you were expecting it is worth to have a look in these files to make sure your interesting voxels were even analyzed. If they weren't you may consider repeating the analysis with less groups (for example if only the third group has no patient with lesions in this particular voxel) or, unfortunately, your dataset is not adequate to answer your question.

Furthermore, you will find a .mat-files (*for_result_tool.mat*) in your result folder. This file is needed for the NIX display tool. If you plan not to use this tool you can delete the file. Otherwise, it has to stay.

2.4 Result Displaying

The tool for result displaying was especially developed for the NIX toolbox. It will not work for any other displays or if you renamed, relocated or deleted (single) files from the result folder.

4.1. After your calculations are finished the tool will start automatically. If you want to start it manually, change your Matlab path to the folder where you extracted the NIX-Toolbox and type in the Matlab Command Window: *nix_show_results* and press Enter. Now choose the folder of the results you wish to display.

4.2. If SPM is not detected you will be asked to locate it. If you do not have it you can download it for free.

4.3. You are asked for an underlying anatomical picture. You may choose any NII-file you want. The file will be stored in the result folder and if you start the display tool in the future it will be detected and you will be asked to either use *the previous one* or to select a *new one*. If chosen, the *new one* will override the *previous one*.

4.4. You are asked for an atlas file that that will characterize the significant clusters. Your SPM folder will be searched for *atlas71.nii*. If it was found or you loaded an(other) atlas file in a previous session for these results, you will be asked if you want to choose the *previous/standard atlas*. If there is, the previous atlas will be loaded. If there isn't the *atlas71.nii* file will be loaded. If both do not apply you have to choose one manually. The atlas has to be a nii-file and there has to be a corresponding (same file name) txt-file that defines the regions. You can also close this window without severe ramifications. The atlas file is copied and stored to the result folder.

4.5. The *results tool* will appear. In the following, all parts of the *results tool* will be explained with the help of Fig. 2.4.1 and 2.4.2. The last indices correspond with the indices in the figures (i.e. 4.5.8. describes what is depicted in Fig. 4.1, Box 8).

4.5.1 The results are depicted for the present layer. The blue crosshairs indicate the current position. A *click* on the pictures will shift the current position to the clicked one.

4.5.2 The colorbar indicate the value range.
Note that in Fig. 2.4.1 there is a unipolar colorbar due to F-values are always positive whereas in Fig. 2.4.2 there is a bipolar colorbar due to positive and negative results of the difference scores, see 2.3. Results.

4.5.3 The coordinates of the current position are shown. Any change will shift the current position to the entered one.

4.5.4 The color-coding is defined here. Max. Transp. (maximal transparency) determines how transparent the results of the analysis is depictured on the underlay (0 = no activation is visible, 1 = the activation is fully visible, the underlying picture is invisible). Min. (minimal threshold) from zero to this value the transparency rises constantly from zero to the Max. Transp. value (i.e. in Fig. 11 the transparency is 0 at an F-value of 0 and rises constantly until it becomes 0.8 at a F-value of 4). Max (maximal threshold) the maximum of the colorbar, anything above is presented in the same color (white, top of the colorbar).

4.5.5 Values for contour preferences (see also 4.3.8.). For further information, please see the help section or manual of *spm_bwlabel*. Uncorr p-thres: Threshold for the contour (black line Fig 4.1 and 4.2, Box 1) of the uncorrected p-value image. FDR-p-thres: Threshold for the contour (green line Fig 4.1 and 4.2, Box 1) of the FDR corrected p-value image.

4.5.6 * All former calculations were strictly separated for every voxels. If you want to compare the effects several voxels with each use this. For further information see chapter 2.5.

4.5.7 Selection of the presently shown results for main effects, interactions and post-hoc results (see 2.3. Results for further explanations).

4.5.8 List of the detected clusters and their peaks. A click on one of them will center the image on the respective peak. If you change the present voxel by pressing on the images (see 4.5.1) or enter them (see 4.5.3) this box will indicate to which cluster the present voxel belongs (afterwards, a press on the highlighted entry will, therefore, bring you to the peak of the cluster of the currently selected voxel).

4.5.9 F-, uncorrected p- and corrected p-values for the current position. *pFDRadj = n.c.* indicates that your chosen nominal FDR threshold (see 1.11) lead to an exclusion of the present voxel for the FDR-adjustment. Therefore, there is no FDR-adjusted value.

4.5.10 The data for the current main effect/interaction is plotted. In contingency tables, the numbers of subjects for single groups are bar-plotted. In ordinal data there will are boxplots for the ranks. Note that for post hoc tests (see Fig 12) the data for the whole interaction is plotted and the data for the present post hoc effect is depictured in red boxplots.

4.5.11 Saves the content of box 8 into a text file that is created in the result folder.

4.5.12 * Saves the content of the *Matlab Command Window* into a text file that is created in the result folder.

4.5.13 Saves the raw data and the ranks that were inserted into the analysis as text file which is created in the result folder. This is meant e.g. for fancy plotting in your publication. The lesion information is saved for the present voxel as well as for the typical lesion for every person for the present cluster (cf. Tab. 2.1).

Tab. 1.1. * This table contains descriptive statistics for the present voxel (which refers to the plot of 4.5.10). This table is shown in the *Matlab command window.*
Note: If you selected a Post-Hoc image (see 4.5.7, i.e. Fig. 4.2) the descriptive statistics of all factor levels are displayed and the present factor levels (resp. black bars in 4.3.10) are marked with a *.

Tab. 1.2. * This table contains the pairwise comparisons of every level for the present voxel. The numbers (i.e. 1-12) correspond to the descriptive statistic (Tab. 1) first column as well as the boxplots in 4.5.10. The upper right part of the table contains the within tests, the lower left part the between tests (Brunner-Munzel-Test). For every post hoc test the appropriate test is chosen automatically and the respective other part of the table contains no value. For within-subject tests the standard *nparLD* test (ld.f1) is chosen, for between-subject tests the Brunner-Munzel-test. You find this table in the *Matlab command window*.

Tab. 2.1. * This table contains the descriptive statistics for the typical distribution in all voxels of the present cluster. (see chapter 2.6 for description

Tab. 2.2. * This table contains the pairwise comparisons for the typical distribution in all voxels of the present cluster (see chapter 2.6 for description).

* This is not available for analyses of contingency tables.

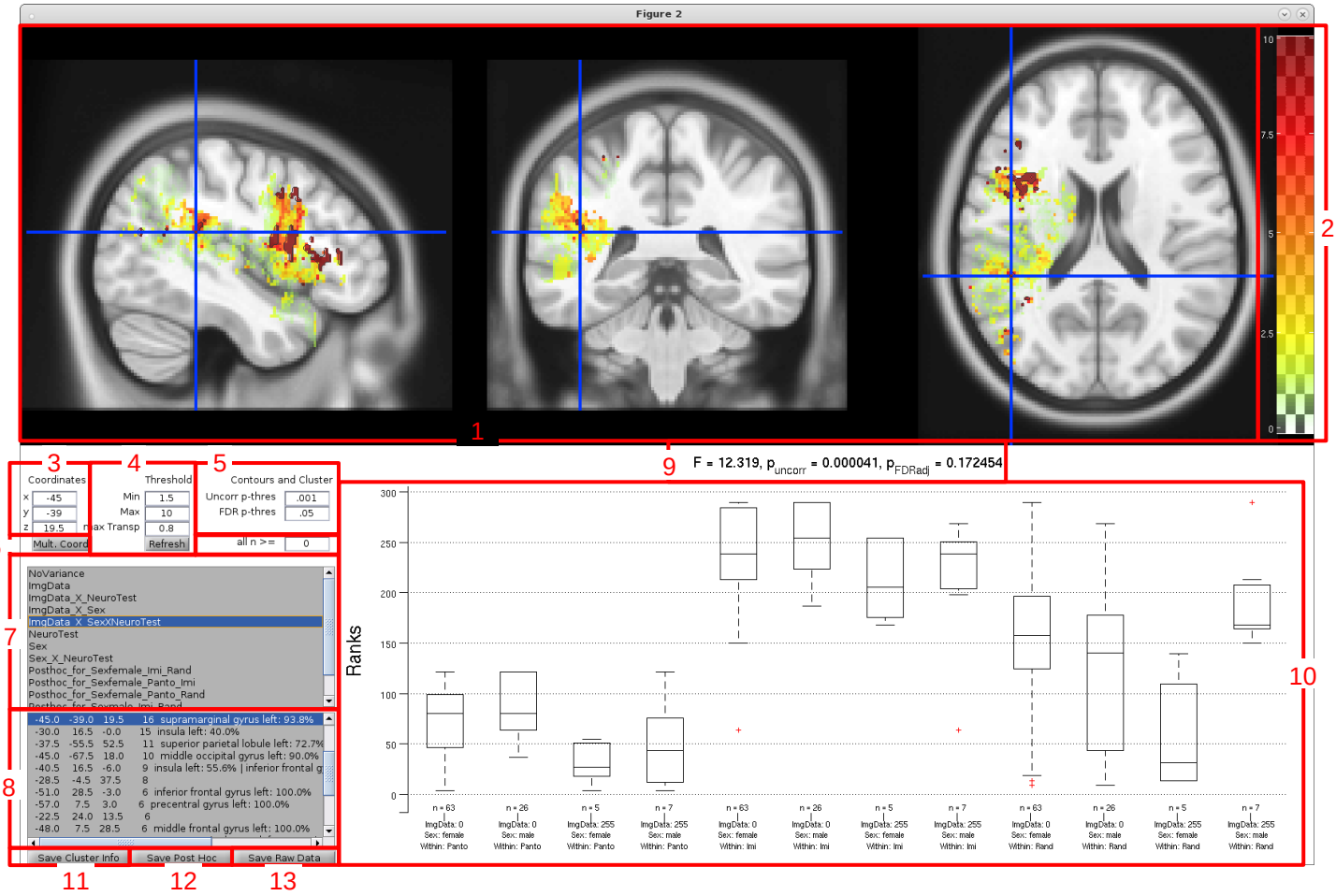


Fig. 2.4.1: The *result tool* with a typical visualization for the result of an interaction in *repeated non-parametric data*. Explanation in 2.4.

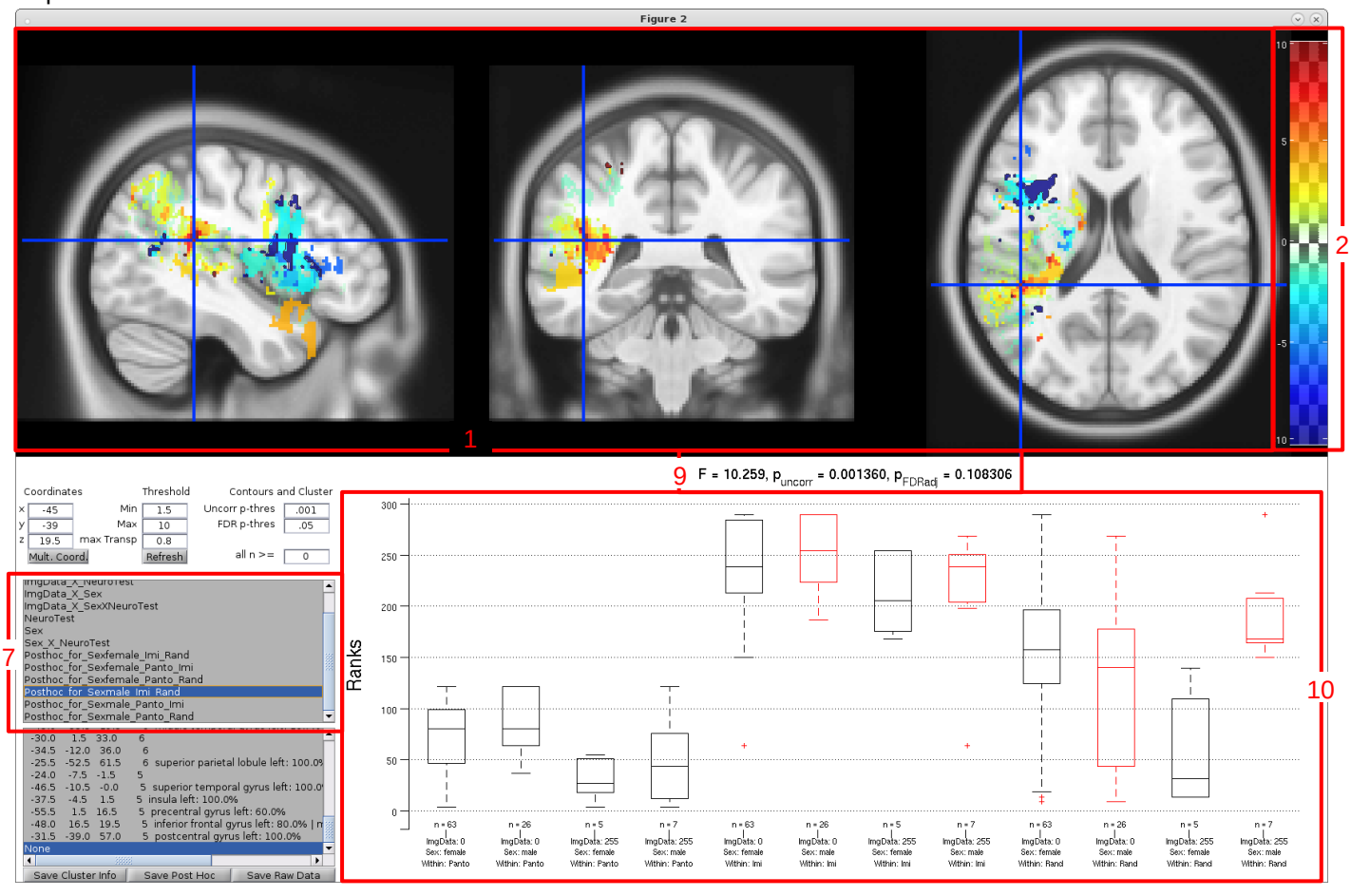


Fig. 2.4.2: The *result tool* with a typical visualization for the post hoc contrasts. See also 4.3.

Voxel -45.0 -39.0 19.5

Tab. 1.1.

Descriptives

#	ImgData	Sex	Within	Median	N
1	0	1	Panto	81	63
2	0	2	Panto	81	26
3	255	1	Panto	28	5
4	255	2	Panto	44	7
5	0	1	Imi	239	63
6	0	2	Imi	255	26
7	255	1	Imi	206	5
8	255	2	Imi	239	7
9	0	1	Rand	158	63
10	0	2	Rand	141	26
11	255	1	Rand	32	5
12	255	2	Rand	168	7

Tab. 1.2

Posthoc Tests

Within Test

	1	2	3	4	5	6	7	8	9	10	11	12
1	----------	.	.	.	0.000***	.	.	.	0.000***	.	.	.
2	0.254	----------	.	.	.	0.000***	.	.	.	0.046*	.	.
3	0.000***	0.000***	----------	.	.	.	0.000***	.	.	.	0.572	.
4	0.166	0.066	0.481	----------	.	.	.	0.000***	.	.	.	0.000***
5	.	0.000***	0.000***	0.000***	----------	.	.	.	0.000***	.	.	.
6	0.000***	.	0.000***	0.000***	0.384	----------	.	.	.	0.000***	.	.
7	0.000***	0.000***	.	0.000***	0.154	0.089	----------	.	.	.	0.000***	.
8	0.004**	0.014*	0.000***	.	0.273	0.128	0.716	----------	.	.	.	0.057
9	.	0.000***	0.000***	0.000***	.	0.000***	0.015*	0.025*	----------	.	.	.
10	0.020*	.	0.003**	0.005**	0.000***	.	0.001***	0.006**	0.148	----------	.	.
11	0.627	0.454	.	0.836	0.000***	0.000***	.	0.000***	0.000***	0.038*	----------	.
12	0.000***	0.000***	0.000***	.	0.043*	0.024*	0.288	.	0.108	0.003**	0.000***	----------

Between Test

General for Cluster

Tab. 2.1.

Descriptives

#	ImgData	Sex	Within	Median	N
1	0	1	Panto	81	62
2	0	2	Panto	81	27
3	255	1	Panto	26	6
4	255	2	Panto	41	6
5	0	1	Imi	239	62
6	0	2	Imi	255	27
7	255	1	Imi	206	6
8	255	2	Imi	232	6
9	0	1	Rand	161	62
10	0	2	Rand	145	27
11	255	1	Rand	66	6
12	255	2	Rand	168	6

Tab. 2.2.

Posthoc Tests

Within Test

Between Test	1	2	3	4	5	6	7	8	9	10	11	12
1	----------	.	.	.	0.000***	.	.	.	0.000***	.	.	.
2	0.223	----------	.	.	.	0.000***	.	.	.	0.024*	.	.
3	0.000***	0.000***	----------	.	.	.	0.000***	.	.	.	0.322	.
4	0.008**	0.001***	0.672	----------	.	.	.	0.000***	.	.	.	0.000***
5	.	0.000***	0.000***	0.000***	----------	.	.	.	0.000***	.	.	.
6	0.000***	.	0.000***	0.000***	0.380	----------	.	.	.	0.000***	.	.
7	0.000***	0.000***	.	0.000***	0.065	0.026*	----------	.	.	.	0.000***	.
8	0.015*	0.039*	0.000***	.	0.115	0.034*	0.887	----------	.	.	.	0.145
9	.	0.000***	0.000***	0.000***	.	0.000***	0.004**	0.065	----------	.	.	.
10	0.014*	.	0.000***	0.002**	0.000***	.	0.000***	0.024*	0.227	----------	.	.
11	1.000	0.763	.	0.385	0.000***	0.000***	.	0.003**	0.005**	0.101	----------	.
12	0.000***	0.000***	0.000***	.	0.075	0.052	0.185	.	0.236	0.020*	0.000***	----------

2.5 Statistical Comparison of multiple Coordinates

You looked at your results and found one brain area to be associated with one dependent measurement (e.g. a test score) and another brain area with another dependent measurement (e.g. a different test score). You found the interaction effect in both significant. However, to prove e.g. a double dissociation you would be required to test both (or more) voxels in one statistical model (e.g. NeuroTests×Lesion×Voxel). This is also implemented in the NIX-Toolbox.

To compare multiple voxels in the same model, press button 6 in Fig. 2.4.1 (4.5.6). The figure 2.5.1 will appear.

I1 How many voxel do you want to compare. At least 2 – open end. The field I2 will change accordingly.

I2 Insert the voxel you want to compare. (for example the peak voxels of the first two clusters)

I3 This field changes according to your design entered in step 2.1. You choose what different factors you want to have considered in this analysis.

I4 Perform the calculation. The results are illustrated subsequently. You find them in the *Matlab Command Window*.

I5 After calculation (I4), you may save the output of the *Matlab Command Window* to a text file that will be saved in the result directory.

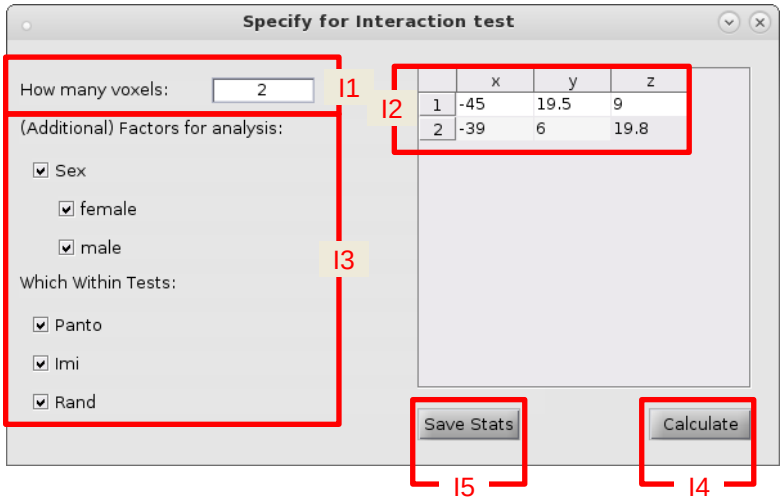


Fig. 2.5.1. The Statistical Comparison of multiple voxels.

O1 The analysis will be performed twice. Once for the exact voxels you entered (O1.1) (e.g. the peak voxels of two cluster), and once for the typical clusters distribution (O1.2) (see 2.6). If the chosen voxel does not belong to a cluster the particular voxel is utilized (there will be indicator in O2.2 and O4.2)

O2 The presently chosen voxels (O2.1) resp. clusters (O2.2).

O3 A list of the sample sizes for the whole design (changes with the choice of I3) for the present voxels (O3.1) resp. cluster (O3.2).

O4 A description of the test performed. The appropriate test is chosen automatically. Here you also find the reason why the performed test was the appropriate one.

O5 The results of the test for the specific voxels (O5.1) resp. clusters (O5.2).

```
_____________________________________________________

  Calculating Interaction effects for multiple voxels
_____________________________________________________

------------ Voxel Comparison ------------   O1.1

COORDINATES:

              x       y       z
Voxel#01:   -45.0    19.5     9.0
Voxel#02:   -39.0     6.0    19.5
```

O2.1

```
DESCRIPTIVES:
   Sex        Voxel#01   Voxel#02     Number
-------------------------------------------
female               0          0         64
                     0        255          1   # excluded
                   255          0          0   # excluded
                   255        255          3

  male               0          0         29
                     0        255          1   # excluded
                   255          0          1   # excluded
                   255        255          2
```

O3.1

```
TEST DESCRIPTION
Voxels were modelled only as one factor because:
- at least one group had fewer than 2 people
- you also wanted a between factor to be considered
- There were voxels that had to be excluded due to insufficient sample sizes, therefore, no full
crossed design was available
```

O4.1

```
RESULTS
-------------------------------------------------
              Effect   F-value      df   p-value
-------------------------------------------------
               Voxel     0.553    1.00   0.45716
           NeuroTest   613.589    1.97   0.00000 ***
     Voxel:NeuroTest    14.848    1.97   0.00000 ***
                 Sex     0.014    1.00   0.90682
           Voxel:Sex     0.468    1.00   0.49388
       Sex:NeuroTest    44.727    1.97   0.00000 ***
 Voxel:Sex:NeuroTest    54.915    1.97   0.00000 ***
_________________________________________________
```

O5.1

```
------------ Cluster Comparison ------------
```

O1.2

```
COORDINATES:
             x      y      z
Voxel#01:  -45.0   19.5    9.0
Voxel#02:  -39.0    6.0   19.5
```

O2.2

```
DESCRIPTIVES:
   Sex        Voxel#01   Voxel#02     Number
-------------------------------------------
female               0          0         61
                     0        255          4   # excluded
                   255          0          1   # excluded
                   255        255          2

  male               0          0         29
                     0        255          1   # excluded
                   255          0          1   # excluded
                   255        255          2
```

O3.2

```
TEST DESCRIPTION
Voxels were modelled only as one factor because:
- at least one group had fewer than 2 people
- you also wanted a between factor to be considered
- There were voxels that had to be excluded due to insufficient sample sizes, therefore, no full
crossed design was available
```

O4.2

```
RESULTS
-------------------------------------------------
              Effect   F-value      df   p-value
-------------------------------------------------
               Voxel    16.234    1.00   0.00006 ***
           NeuroTest   618.368    1.94   0.00000 ***
     Voxel:NeuroTest    15.027    1.94   0.00000 ***
                 Sex     3.629    1.00   0.05677 .
           Voxel:Sex     0.274    1.00   0.60049
       Sex:NeuroTest    40.395    1.94   0.00000 ***
 Voxel:Sex:NeuroTest    55.210    1.94   0.00000 ***
_________________________________________________
```

O5.2

2.6 Cluster Analysis and Information

When selecting a peak cluster of a voxel (by selecting something in 4.5.8) this voxel has the highest F-value in the whole cluster. However, this voxel is often misleading because it is not representative for the whole cluster (you have to become suspicious when the peak voxel is at the very border of your cluster). Therefore, besides your post-hoc statistics (Tab. 1.2.) for this particular voxel, you will also get a post-hoc tests for the cluster (Tab. 2.2.) as well as the multiple voxel comparisons are calculated for the cluster.
How the cluster group is assigned: For every person all voxels of the cluster are checked. If the majority of the voxels have lesions in it, the person is assigned to the lesion group (otherwise to the non-lesion group).

3. What analysis do I have to choose and what do I have to consider regarding my data?

The question is what does your dependent data look like:

- nominal (you have only groups but no distributed data. For example you have patients that have aphasia and you have patients that have neglect. Now you want to look whether there are voxels that are specific for each of the syndromes.)
  → *Contingency Table*
  Consider: Check that your contingency table has no zeros/empty cells! (That means you need patients that have both neglect and aphasia, some that have only aphasia, some that have only neglect, and some that have neither aphasia nor neglect). Otherwise your effects will go completely haywire.

- ordinal (you have distributed data. All your patients performed a test and could score between 0 and 40)
  - you only have one dependent measurement (e.g. all your patient took one performance test and now you want to look whether there is a neural correlate to this test)
    → Sorry, you have to use MRIcron. On the bright side, its free. The NIX-toolbox was created to extend the features of MRIcron. Therefore we did not implement the already available features.

  - you have at least two dependent measurements (e.g. all your patients took two or more performance tests)
    → *Repeated non-parametric data*
    Consider: All of the tests have to scale equally. (that means the maximal achievable score of all of yours tests have to roughly the same) If your tests aren't, scale them manually (e.g. divide all values of a test by the maximal achievable score of this particular test then multiply it by 10. Do this with all your tests and you will have scaled them equally to 10). Otherwise, this will spoil your interaction effects.

4. ANOVA-type vs. Wald-type statistics

This is a very brief summary of the advantages and disadvantages between the Wald- and the ANOVA-type statistics (see Brunner, E., Domhof, S., & Langer, F. (2002). *Nonparametric Analysis of Longitudinal Data in Factorial Experiments*. New York: Wiley.)
The **ANOVA-type** statistic has the disadvantage of possible efficiency loss compared to the Wald-type. However, this only applies to very large sample sizes and a high amount of within factor levels. In case of numerous within factor levels the ANOVA-type statistics become more conservative. In summary, it is recommended to use the ANOVA-type statistics.
In small sample sizes, the **Wald-type** statistics may lead to anti-conservative decisions. This statistic should only be used in designs with small degrees of freedom (i.e. few within factor levels) or when extremely large samples ($n_{group} > 200$) are available and groups are homogeneous. In the

case of this toolbox, groups also mean lesioned vs. non-lesioned patients for every voxel. It is highly unlikely guaranteeable that lesioned vs. non-lesioned groups are homogenous for every voxel. Therefore, it is **not** recommended to use the Wald-type statistic.

5. Trouble-Shooting

All known errors and bugs are fixed in the current version. If you find some, please report them (current e-mail address kai.nitschke@uniklinik-freiburg.de)

6. System Requirements

Linux

- installed Matlab (http://www.mathworks.de/products/matlab/), license required
  - NIX was developed on *Matlab R2012a x64* for Linux
- installed SPM (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), *free*
  - NIX was developed on SPM8 in Linux (and tested on SPM12)

Windows

- installed Matlab (http://www.mathworks.de/products/matlab/), license required
  - NIX was tested on *Matlab R2012a x64* on Windows 10
- installed SPM (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), *free*
  - NIX was tested on SPM8 on Windows 10

Mac

- installed Matlab (http://www.mathworks.de/products/matlab/), license required
  - NIX was tested on *Matlab R2014a x64* on Mac OS X
- installed SPM (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), *free*
  - NIX was tested on SPM12 on Mac OS X

The NIX toolbox was developed on the following system:

Dell Optiplex 9020

- Gnome 2.32.1, Kernel Linux 3.10.25
- 3.4 Ghz Intel Core i7-4770
- 16 GB DDR3 SDRAM with 1600 Mhz
- Intel Integrated Graphics

The NIX toolbox was also tested on the following systems:

Lenovo ThinkPad E530

- Windows 8 x64
- 2.20 Ghz Inter Core i7-3632QM Ivy Bridge, 6Mb Cache
- 8 GB DDR3 SDRAM with 1600 Mhz
- NVIDIA GeForce GT 635M with 2 GB RAM / Inter HD Graphics 4000

Apple Mac Book Pro

- Mac OS X 10.9.5 (Mavericks)
- 2.26 Ghz Inter Core 2 Duo, 3 MB L2-Cache

- 2 GB DDR3 SDRAM with 1066 Mhz
- NVIDIA GeForce 9400M with 256 MB DDR3 SDRAM (shared with main RAM)