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Self-learning classification of fMRI data with the CLASSIF1 software – an example with somatoform pain disorder

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Summary

The aim of this study concerned the individual discrimination between patients with somatoform pain disorder and healthy controls by automated classification of cerebral fMRI activation patterns.

This was achieved by applying a series of alternating noxious and innocuous tonic heat stimuli on the inner side of the left forearm to a group of female patients and gender and age matched healthy controls during fMRI scanning. The entire fMRI data time-series included noxious, innocuous and resting conditions. The data was classified following extraction and scaling of the time series of mean fMRI BOLD signals of 90 defined AAL ROIs with the SPM2 Marsbar Toolbox. The concatenated time-series of all ROIs for each patient was classified by the CLASSIF1 software (Valet,1993) using 10 randomly selected patients and 10 controls as learning set with 3 patients and 3 controls as unknown test set (hold-out validation).

Classification accuracy was 92.3% (1 misclassification, each in the learning and test set). Discriminating differences of fMRI-BOLD signals between patients and controls were found in memory relevant brain structures, such as amygdala, fusiform cortex, parahippocampus, as well as the temporal cortex.

CLASSIF1 classification allows accurate discrimination of individual patients from healthy controls with the new potential to elaborate interlaboratory standardized, hypothesis and model free fMRI data classifiers.

Introduction

A changed cerebral processing of pain stimuli has been evidenced by fMRI for

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***** LEARN *****
(MICH1.TXT measured values 325 data points/brain area,3sec/point, 0.0 -> 0.0010)
-------------------------------------------------------------------------------
| NR. |CLASSIFIER CATEGOR. |CATEGORY ABBREVIAT. |COIN|CLASSIFIER MASKS          |
-------------------------------------------------------------------------------
|   1 |control             |C                   |1.00|00000000000000000000000000|
|   2 |pain                |P                   |1.00|--------------------------|
-------------------------------------------------------------------------------
-------------------------------------------------------------------------------
| REC.|DATAB:  SLLEARN.BI4 |                    |CLAS|SAMPLE CLASSIF.MASKS      |
| NR. |RECORD LABELS       |CLASSIF1-CLASSIFIC. |COIN| . = no value             |
-------------------------------------------------------------------------------
|   1 |MI002.C.............|C                   |1.00|00000000000000000000000000|
|   2 |MI003.C.............|C                   |1.00|00000000000000000000000000|
|   3 |MI004.C.............|C                   |1.00|00000000000000000000000000|
|   4 |MI007.C.............|C                   |1.00|00000000000000000000000000|
|   5 |MI008.C.............|C                   |1.00|0000000000000000000000000+00|
|   6 |MI009.C.............|C                   |1.00|00000000000000000000000000|
|   7 |MI011.C.............|C                   |1.00|00000000000000000000000000|
|   8 |MI014.C.............|C                   |1.00|00000000000000000000000000|
|   9 |MI015.C.............|C                   |1.00|0++00+0+0000000000000000000|
|  10 |MI016.C.............|C                   |1.00|+00++0+0++++++++++++++0++|
-------------------------------------------------------------------------------
|  11 |MI023.P.............|P                   | .92|---------------0---------0|
|  12 |MI024.P.............|P                   | .65|-0000--------0-00------00-|
|  13 |MI025.P.............|P                   | .77|---------------0---00--000|
|  14 |MI029.P.............|P                   |1.00|--------------------------|
|  15 |MI031.P.............|P                   | .92|-----------------------0+|
|  16 |MI032.P.............|P                   | .77|----------00----00---00--|
|  17 |MI033.P.............|P                   |1.00|--------------------------|
|  18 |MI037.P.............|P                   | .96|-----------------0-------|
|  19 |MI038.P.............|P                   |1.00|--------------------------|
|  20 |MI039.P.............|C                   |1.00|+++++0000++++++0+00+++0+00|
-------------------------------------------------------------------------------
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Figure 1 Legend: Controls (C) and pain patients (P) (column 2) of the learning set are correctly (column 3) classified in most instances by an optimally discriminating data pattern of 26 parameters (column 5). The classifier masks (top part of the figure) represent the most frequently found triple matrix character ("-", "0", "+") for the (C) and for the (P) learning set. The classification coincidence factor (column 4) indicates the fractional coincidence of each sample (control or patient) classification mask with the (C) and (P) classifier masks. One patient (MI039) is misclassified.

functional somatic syndromes like fibromyalgia, irritable bowel syndrome or pain disorder (Gündel, 2008). Usually, such fMRI studies are hypothesis driven, focus on task related cerebral activation changes and obtain results on a group level. To bypass these limitations, we used a hypothesis and model free classification approach.

The earlier developed multiparameter classification software CLASSIF1 (Valet, 1993) was adapted to the analysis of fMRI time sequences (task- and rest conditions). The performance of the software was assessed in this study by discriminating pain patients and healthy controls from fMRI patterns at a single subject level.

Materials and methods

The cerebral pain processing of 13 female patients with somatoform pain disorder (age range: 29-59 years) and 13 gender and age matched healthy controls was investigated with fMRI (EPI technique: 325 Images, TE 50ms, TR 2510ms, 3x3x5mm).

Subjects received a series of alternating noxious and innocuous heat stimulation on the inner side of the left forearm (sequence of 8 blocks, each with 40 sec noxious, 20

sec neutral, 40 sec innocuous, 20 sec neutral thermal stimulation; protocol according to Lautenbacher, 1995) during fMRI scanning. Thermal stimulation was applied with a Peltier thermode of the Medoc TSA I system.

The fMRI data was preprocessed with realignment, normalization and smoothing using the SPM2 software. After this, the time series of the mean fMRI BOLD signal of 90 defined AAL ROIs (Automated Anatomic Labeling; Tzourio-Mazoyer, 2002) were extracted and scaled with the SPM2 Marsbar Toolbox for every subject. Then, the time-series of the 90 AAL ROIs were concatenated separately for each subject (90 ROIs x 325 time points=29250 data columns).

Ten patients and 10 controls were selected as learning set for classification (20 rows) by the CLASSIF1 software. The validation occurred with the remaining 3 patients and 3 controls as unknown test set (hold-out validation).

The CLASSIF1 software performed a single time point analysis of a 29250 columns (90 regions x 325 time points) by 20 rows (20 subjects) data matrix. The classification analysis comprised three steps:

First, the 10% and 90% percentiles of fMRI BOLD signals of controls are determined for each time point. Second, the time points between the 10% and 90% percentiles are transformed for controls and patients into „0“ (=within limits), into „-“ below the 10% percentile (decreased) and into „+“ above the 90% percentile (increased) to establish the triple matrix classification database. Third, the most discriminatory data columns between patients and controls were iteratively determined to obtain the best classifier masks for the classification of each sample in the learning set.

The learning process was repeated with percentile pairs 15-85%, 20-80%, 25-75% and 30-70% to further optimize the classifier masks. However, the highest discrimination was achieved for the 10-90% percentile pair (Figure 1).

Subsequently, the unknown test set was classified with the obtained classifier masks of the learning set (Figure 2).

Results

The classification accuracy of the CLASSIF1 algorithm was 92.3%. One misclassification occurred in the learning (Figure 1) and one in the unknown test set (Figure 2).

The discriminating fMRI-BOLD signals between patients and controls correspond to memory relevant brain structures, such as the left amygdala, the left fusiform cortex, the right parahippocampus, as well as the right temporal pole. These results are similar to findings of our recent fMRI study investigating task related changes (=noxious stimulation) in the same patient group (Gündel, 2008).

Conclusions

The CLASSIF1-algorithm permits to accurately discriminate individual patients from controls. With its single time point analysis (column by column approach) the algorithm provides essential temporal and spatial information concerning the discriminating differences on a whole brain level in a hypothesis and model free approach. The classifiers are suitable for interlaboratory data classification as a precondition for the elaboration of standardized fMRI classifiers.

NR.	CLASSIFIER CATEGOR.	CATEGORY ABBREVIAT.	COIN	CLASSIFIER MASKS
1	control	C	1.00	00000000000000000000000000
2	pain	P	1.00	----------

REC. NR.	DATAB: SLLEARN.BI6 RECORD LABELS	CLASSIF1-CLASSIFIC. - =unkn.smple <.65	CLAS COIN	SAMPLE CLASSIF.MASKS . = no value
1	MI001.?.....	C	1.00	+0000++0+00+++00++++++++++
5	MI005.?.....	C	.85	00000---0000000000-0000000
10	MI012.?.....	C	1.00	00+0+0+0+000++++++++++0++
14	MI022.?.....	P	.85	---------------0--0-----00
18	MI027.?.....	C	1.00	00000000000000000000000000
23	MI035.?.....	P	1.00	----------

Figure 2 Legend: The unknown test set of controls (C) MI001/005/012 and pain patients (P) MI022/027/035 (column 2) are classified as (C) or (P) (column 3). This is achieved by determining the highest positional coincidence of their respective classification mask (column 5) with either the (C) or (P) classifier masks from the learning set. One patient (MI027) is misclassified. Triple matrix characters "-" represent positional hits for (P) while "0" and "+" characters are hits for (C).

Further studies will address the issue whether task-related or resting-state fMRI studies are better suited for the discrimination between patients and healthy control subjects.

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