Mirror visual feedback therapy for phantom pain: changes in functional connectivity patterns

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Purpose

Mirror visual feedback therapy (MVFT) offers efficient non-invasive treatment for patients suffering from phantom limb pain. It is hypothesized to cause functional remodeling of neural networks in the patients brain. We evaluate subject-specific functional parcellation of fMRI data and subsequent model map analysis to quantify changes of functional connectivity patterns related to MVFT.
Methods and Materials

The medical data consists of BOLD functional MR acquisitions using a Philips 1.5 Tesla MR scanner with sequence: TE=50ms, TR=3616ms, matrix=96mmx78mm, 100 dynamics, 36 slices, acquisition time 6min. fMRI data was recorded from 5 patients, suffering from left sided lower extremity phantom limb pain, before and after the MVFT. A block design and a simple motor paradigm was used, comprising a rhythmic repetitive flexion/extension (f=1Hz) movement in the intact ankle. Moreover the patients were asked to perform flexion/extension movements in their phantom amputated ankle joint, without visual control of their movements. 5 periods of lower limb movements lasting 36 seconds were followed by 5 periods (36 seconds) of rest. During the rest condition the patients were asked to relax and not to mentally rehearse the movements. Both lower extremities were examined separately. In order to control for heterogeneity of phantom movements and for movements in other lower limb joints, the patients rehearsed the movements in the presence of a physician prior to the fMRI examination in the scanner. The operator monitored the movements and performance of the patients and controls during the examination.

For further analysis, only the fMRI acquisitions of the performed flexion/extension movements in the phantom amputated ankle joint were used. Standard fMRI data preprocessing was achieved with the SPM8 software. It consisted of co-registration, motion correction, spatial normalization to the MNI template space and re-interpolation to 3x3x3mm³ voxel size. The final preprocessing step was the computation of the functional information parameters $#(v)$ for every voxel $v$, using a GLM analysis of the data.

Mirror Visual Feedback Therapy:

All study participants underwent a total of 12 sessions of MVFT. The sessions were performed at the Department of Neurology, Medical University of Vienna twice a week (2 sessions per day separated by 2 hours) for 3 weeks. During the study period pain medication remained unchanged in patients. For the MVFT a mirror measuring 77 cm in length and 58 cm in width was aligned in the sagittal plane of each subject, with the intact lower limb placed to one side 15 centimeters from the mirror. Thereby the patients were able to look down on the mirror and see a virtual limb. The amputated limbs were placed behind the mirror to be invisible. The patients were asked to place their intact limbs in front of the mirror, direct their gaze onto the mirror image of their intact limb and mentally align their phantom with this image. The patients were instructed by a physical therapist to carry out a definite set of movements in a structured manner (each exercise done for one minute with a 1 minute break between each exercise) while watching the movement in the mirror. Each session lasted between 26 and 31 minutes. All MVFT sessions were performed under supervision of an experienced physical therapist.
**Parcellation:**

Functional parcellation based on spectral clustering [3] was performed on all fMRI data. A multidimensional scaling representation $E$ of the spatial and functional neighboring relations of every voxel $v$ is established in order to obtain functionally homogenous subject-specific regions of interest. These subject-specific, but between subjects comparable, parcels, adapt to the anatomical and functional characteristics of each subject. For further analysis, each parcel is treated as a voxel by computing the mean BOLD signal of all the voxels belonging to a parcel. For the 200 resulting subject-specific parcels [4], we included only those with at least 25% overlap with the motor and pain processing relevant Brodmann areas (BA: 1-7, 9, 10, 13, 14, 24, 25, 29-33, 39, 40, 46 and 47). This reduces the initial number of 200 parcels to 80 (Figure 1 on page 5), thus leading to a total of 3160 functional connections.

**Functional Connectivity Quantification:**

Functional connectivity patterns among the resulting regions were quantified using the model map algorithm [1] (Figure 2 on page 5). First, the method establishes pairwise relations between all the BOLD signals of the parcels. Based on this set of mutual relations, a Markov chain and consequently a corresponding diffusion map is built. These model maps embed the functional interactions between all parcels into a metric space, where the Euclidean distances relate to the co-dependencies of the fMRI signals.

**Feature Selection:**

The quantified functional connectivity values serve as connectivity pattern for a classification task between pre- and post-therapy condition. A Gini importance ranking of the connections is derived from a random forest classifier [2] trained to differentiate between pre- and post-therapy pattern. It identifies the multi-variate pattern of functional connections with the highest differentiating power. We evaluate the classification performance, and the stability of the connection selection (overlap of top-ranked connections) in a leave one fMRI acquisition out cross-validation (LOOCV). The connections of the training set (9 fMRI acquisitions) are ranked by the Gini importance, the top $i$ features, with $i = 1, ..., N$, are kept and a classifier is trained on the resulting descriptors. The remaining pre- or post-therapy fMRI acquisition is then classified by this classifier. 10 iterations of LOOCV were performed, where every single data set was used as the test set once. We validate the method by calculating the classification accuracy. To evaluate the consistency of the feature selection, the average dice coefficient between the $i$ preliminary top ranked features and the $i$ top ranked features of every training set is computed.
Images for this section:

**Fig. 0:** The 80 Brodmann area relevant parcels used for analysis. Colors are for delineation purpose only.

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**Fig. 0:** Generating a model map from fMRI data.

Results

The classification accuracy reached up to 80% using the 80 relevant parcels from a parcellation sized 200. The average dice coefficients increase rapidly and reaches 60% as far as 27 features are selected. Figure 1 on page 7 displays a comparison of the average dice coefficients from a feature selection process using GINI importance ranking derived from random forests, standard t-test and randomized selection. Naturally, GINI importance rating and a t-test feature ranking outperform a randomized feature selection. Despite the fact that the t-test dice coefficients reach an earlier peak, classification performance is better with the GINI importance feature selection, as shown in Figure 2 on page 7. An inspection of the GINI importance ranking reveals that there is a clear separator between more or less important rated connections (Figure 3 on page 7). We can now select the 27 top rated connections, before the drop in GINI importance, as the connections with the most differentiating power between pre- and post-therapy condition.

We separate these 27 selected functional connections in two groups where one group exhibits stronger connectivity before and the other group after the MVFT. In our experiment 17 functional connections were decreasing (Figure 4 on page 8), while 10 connections are stronger after the therapy (Figure 5 on page 8). Since Euclidean distances in the model maps are used to quantify the functional connectivity: the smaller the value the higher the connectivity. The boxplots cleary show the differentiating power of these 27 selected features.

Figure 6 on page 8 displays the connections which are stronger before the MVFT and Figure 7 on page 9 shows the connections which increase after the therapy. Parcels, part of the functional connections decreasing after the MVFT are mostly located in Brodmann areas 6 and 4, while functional connections stronger after the therapy comprise primary BAs 6, 7 and 32.
Fig. 0: Comparison of the dice coefficients of Gini importance, t-test and random based feature selection.

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Fig. 0: Comparison of the classification performance using Gini importance and t-test based feature selection.

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**Fig. 0:** The drop in Gini importance delineates the functional connections with the most differentiating power between pre and post therapy condition.

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**Fig. 0:** Comparison of the quantifications of the 17 functional connections which are stronger before the MVFT.

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**Fig. 0:** Comparison of the quantifications of the 10 functional connections which are stronger after the MVFT.

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**Fig. 0:** The 17 functional connections which are stronger before the MVFT. Colors are for delineation purpose only.

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**Fig. 0:** The 10 functional connections which are stronger after the MVFT. Colors are for delineation purpose only.

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Conclusion

Functional connectivity analysis based on model maps of subject-specific fMRI parcellation results in dimensionality reduction and a quantitative description of functional connectivity patterns. It allows for group analysis, since anatomical and functional differences between subjects are modeled.

The changes in connectivity patterns during therapy reveal potential neurophysiologic mechanisms of treatment-related pain reduction for phantom limb pain patients. Additionally, the subject-specific functional connectivity measures resulting from the model map algorithm, facilitate classification tasks and can be used to model functional networks.


