Identifying overlapping functional networks in multi-paradigm fMRI studies

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Authors: K.-H. Nenning, V. Schoepf, R. Donner, G. Kasprian, D. Prayer, G. Langs; Vienna/AT
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Purpose

The exploratory analysis of functional brain imaging data reveals a wealth of information regarding functional processes during rest, or during specific experiment conditions. The investigation of functional connectivity structures is a particularly interesting field, since it directly aims at understanding the functional architecture and interconnectedness of a system of distributed units [1, 2]. Currently the majority of functional connectivity studies is based either on resting state data, or a single paradigm, and functional networks are viewed as a partition of the cerebral structure. This is a limitation since there is strong evidence, that it is a system of overlapping networks and units that participate in multiple cognitive processes [3, 4].

In this work we propose a method for joint analysis of shared connectivity structures across multiple experiment conditions. It is aimed to complement single paradigm analysis, gaining better insight into the brains functional organization and to aid paradigm selection and study design.
Methods and Materials

Multiple Relational Embedding

We simultaneously embed the connectivity structures emerging during multiple paradigms (Fig.1) into a single embedding space to learn the underlying joint structure. In this embedding space, each point represents a voxel, or region of interest in the fMRI data. Their distribution is governed by the global functional connectivity structures of all paradigms. The embedding of multiple connectivity matrices is performed based on multiple relational embedding (MRE) [5].

The basic concept of multiple relational embedding is illustrated in Fig. 2. First, the connectivity structures P are quantified for every task-dependent data. These graphs are related to the single joint embedding X via task-specific latent embeddings, defined by a scaling of X with task-specific transformation matrices R. The joint embedding is established by minimizing the differences between these latent embeddings and the specific functional connectivity structures, via a gradient descent to update X and R.

Data

The joint embedding is performed on fMRI data acquired with two complementary language paradigms: phrases, a language processing task, and verb-generation, a language forming task.

FMRI data is acquired from 4 subjects with a Philips 3 Tesla MR scanner (TE = 35 ms, TR = 3000 ms, matrix = 128×128×32 mm, voxel-size 1.8×1.8×4 mm3) with 100 volumes over an acquisition time of 5 minutes. We evaluate the combined analysis of a language-processing and a language-forming paradigm, performed by brain tumor patients during neurosurgical intervention planning. During phrases, the subject is instructed to read semantically right and wrong sentences. Wrong sentences are grammatically correct but the object is semantically inappropriate. During verb-generation, nouns are presented and the subject is asked to think of all verbs which can be associated with the given word. In both paradigms, during the baseline blocks hash signs are shown. Both paradigms are in a block design with five RS (R = baseline/rest, S = stimulus) blocks. Standard fMRI data preprocessing is performed using the SPM8 software package, comprising motion correction, co-registration, normalization to the Montreal Neurological Institute (MNI) template space (3mm³) and grey matter segmentation. Since the initial grey matter mask contains # 60.000 voxels, we perform parcellation into 1000 homogeneously working parcels [6] for computational reasons. General Linear Model (GLM) [7] activation analysis is performed on the resulting parcels, with an activation cut-off of p < 0.05.
Experiments

To validate whether the joint embedding captures shared functional connectivity structure across multiple paradigms, we perform joint embedding of two paradigms. Paradigms A and B each consist of 5 baseline-stimulus blocks. We embed part of A (e.g., z baseline-stimulus blocks resulting in A(z)) and B. We perform standard GLM analysis [7] on A(z) and regularize by either k-nearest neighbors in the anatomical space (MNI), or in the joint embedding space (MRE). Regularization by spatial smoothing is common in fMRI analysis, and was thus chosen as a means for comparison. Note that spatial smoothing is problematic since it results in a loss of activation localization accuracy and may produce false-positive activation results in neighboring voxels [8]. We then compare the two resulting activation maps (regularized by anatomy vs. joint embedding) of the partial sequence A(z) with the activation map of the full sequence A treating the latter as reference, and calculating sensitivity, and specificity. We repeat the experiment for partial sequences B(z) analogously.
Fig. 1: MRE provides a single joint embedding of the functional characteristics evoked by two different fMRI block design paradigms.

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Fig. 2: The basic concept of multiple relational embedding. First, the connectivity structures (P) are quantified for every task-dependent data. These graphs are related to the single joint embedding X via task-specific latent embeddings, defined by a scaling of X. The joint embedding is established by minimizing the difference between these latent embeddings and the specific functional connectivity structure.

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Results

The results for the analysis of phrases are shown in Fig. 3 (sensitivities) and Fig. 4 (specificities). The results for verb generation are displayed in Fig. 5 (sensitivities) and Fig. 6 (specificities).

MRE regularization provides consistently better sensitivity and specificity for all 4 subjects and both paradigms compared to spatial regularization. For phrases and a time-series length of 3 AB blocks, a sensitivity of 0.7 is already reached in the data of 4 subjects, whereas spatial smoothing achieves below 0.6. Sensitivities in verb-generation perform similarly better with up to 0.2 more sensitivity with functional regularization. Functional regularization also results in increased specificity up to 0.2.

Additionally, we compare the joint embedding with a single stochastic neighbor embedding (SNE) [9] of the paradigm of interest. MRE outperforms SNE in terms of sensitivity and specificity, indicating the shared connectivity structure captured in the joint embedding.
Fig. 3: Sensitivities of phrases.

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Fig. 5: Specificities of phrases.

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**Fig. 4:** Sensitivities of verb generation.

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**Fig. 6:** Specificities of phrases.

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Conclusion

We investigate if joint embedding of functional connectivity structures observed during multiple fMRI experiments can capture functional structures shared across paradigms. In an experiment we evaluate if the joint embedding can improve single paradigm activation analysis. Although preliminary, the results indicate that shared connectivity structure observed during multiple paradigms is encoded in the joint embedding. Using the embedding for regularization can augment activation detection in individual experiments, and improves results compared to spatial regularization. Future work will focus on the more in-depth investigation of the structure of the embedding, and the generalizability of the methodology to arbitrary paradigms.
References


