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# Diffeomorphic functional brain surface alignment: Functional demons

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## ABSTRACT

Aligning brain structures across individuals is a central prerequisite for comparative neuroimaging studies. Typically, registration approaches assume a strong association between the features used for alignment, such as macro-anatomy, and the variable observed, such as functional activation or connectivity. Here, we propose to use the structure of intrinsic resting state fMRI signal correlation patterns as a basis for alignment of the cortex in functional studies. Rather than assuming the spatial correspondence of functional structures between subjects, we have identified locations with similar connectivity profiles across subjects. We mapped functional connectivity relationships within the brain into an embedding space, and aligned the resulting maps of multiple subjects. We then performed a diffeomorphic alignment of the cortical surfaces, driven by the corresponding features in the joint embedding space. Results show that functional alignment based on resting state fMRI identifies functionally homologous regions across individuals with higher accuracy than alignment based on the spatial correspondence of anatomy. Further, functional alignment enables measurement of the strength of the anatomo-functional link across the cortex, and reveals the uneven distribution of this link. Stronger anatomo-functional dissociation was found in higher association areas compared to primary sensory- and motor areas. Functional alignment based on resting state features improves group analysis of task based functional MRI data, increasing statistical power and improving the delineation of task-specific core regions. Finally, a comparison of the anatomo-functional dissociation between cohorts is demonstrated with a group of left and right handed subjects.

## Introduction

Accurate alignment of brain structures is essential for the quantitative comparison of local characteristics across individuals. Anatomical alignment is a standard procedure for fMRI analysis, and has had a substantial impact by enabling location specific comparison of individuals or cohorts (Fischl, 2012). However, relying on macro-anatomy suffers from limitations if the association between anatomy and function is weak. Here, we propose to align imaging data across individuals based on the global functional connectivity structure observed during resting state functional magnetic resonance imaging data (rs-fMRI), while at the same time constraining the transformations to diffeomorphisms on the cortical surface.

The potential dissociation between structure and function has been addressed in only a small number of studies which used functional features for inter-individual alignment (Sabuncu et al., 2010; Conroy et al., 2013; Robinson et al., 2014; Langs et al., 2015). Anatomo-functional dissociation occurs if the variability of functional architecture across subjects cannot be entirely explained by anatomical differences (Mueller et al., 2013; Tootell et al., 1995; Smith et al., 2005; Brett et al., 2002). Group studies that rely on a static anatomical relationship can be biased by reduced spatial overlap of functionally similar regions across individuals and corresponding reduced group-level activation. Individual variability in functional architecture could become more complex if diseases affect both function and anatomy, thus making anatomical alignment more prone to these confounding factors (Brett et al., 2002).

We propose a functional alignment approach based on a diffeo-

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morphic registration of functional resting state features along a spherical projection of the cortical surfaces. The proposed alignment is independent of specific tasks, and uses only rs-fMRI signals as a basis for alignment. We quantify global functional network characteristics by spectral embedding, which provides a functional signature of the entire cortex based on resting state fMRI. In this embedding, each dimension represents different aspects of the rs-fMRI architecture.

Functional alignment enables the separate analysis of functional variability and differences in anatomical location. Alignment based on resting state functional connectivity provides a complementary source for correspondence, and allows for the analysis of task-fMRI experiments based on unified correspondences across individuals. While constraining the alignment to a diffeomorphic surface transform limits the variability the method can capture, it disambiguates possible similarities of connection characteristics in widely distributed regions forming functional networks with an anatomical constraint.

In this work, we test if (1) cortical alignment guided by rs-fMRI information is repeatable across scan sessions, (2) if it captures differences across individuals, (3) if the variability is constant or heterogeneous across the cortex, (4) if this alignment improves group-level task fMRI evaluation, and (5) if it can quantify differences across two cohorts of left- and right-handers.

### *State of the art*

Existing standard registration approaches establish correspondence across multiple individuals by assuming anatomical comparability. Typically, in fMRI studies, spatial normalization is employed to map brain regions to a common template space, e.g., the MNI atlas (Evans et al., 1993). This ensures comparability across different studies and atlas labeling. Volume-based normalization approaches are standard and provided by widely used tools such as FSL (Jenkinson et al., 2012) or SPM (Friston et al., 2007). Non-rigid, volume-based transformation models, such as diffeomorphic demons (Vercauteren et al., 2009) or angular interpolation (Duarte et al., 2013), can account for inter-subject anatomical variability and achieve more accurate anatomical registration. Surface-based registration techniques, such as in FreeSurfer (Fischl, 2012) and Spherical Demons (Yeo et al., 2010), use spherical representations of surfaces and align them based on cortical features such as curvature or sulcal depth. Lombaert et al. (2013a) and Lombaert et al. (2013b) introduced diffeomorphic alignment based on spectral features of cortical anatomy providing a speed advantage over traditional surface based registration techniques. Lombaert et al. (2015) extended the spectral alignment approach and incorporated features based on retinotopy on the visual cortex. While we follow a similar paradigm - using a representation of features in a spectral embedding space - the proposed approach uses the global resting-state connectivity structure instead of anatomical features as a basis for alignment. Current volumetric and surface registration approaches provide highly accurate alignment of the macroanatomy; however, they neglect the variability in function across and within subjects (Tootell et al., 1995; Smith et al., 2005), hampering group-level functional analyses especially when the anatomo-functional association is weak.

Alignment approaches that take functional information into account can improve the correspondence across subjects in group analyses. Sabuncu et al. (2010) proposed fine-tuning of anatomical alignment via non-rigid registration that maximizes inter-subject correlation of fMRI signals recorded during a synchronized movie-viewing stimulus. Similarly, Conroy et al. (2013) used spatial patterns of functional responses to movie stimuli to guide anatomical registration with a focus on areas involved in visual processing. Jiang et al. (2013) introduced a progressive matching of multi-range functional connectivity patterns for spatial normalization, and showed that functional alignment improves the overlap of resting-state networks, such as the default mode network. Extending this approach, Langs et al. (2014) proposed decoupling anatomy from function, and aligned fMRI signals recorded during language tasks in an embedding space, improving the match of corresponding task-activation across individuals. Langs et al. (2015) also identified shared resting-state functional networks despite varying spatial footprints across individuals, by parcellation in a population-level embedding space. Nenning et al. (2015) addressed noise during group-wise alignment in the embedding space by a joint-diagonalization approach. By assuming a single activation peak whose position varies across individuals, Gramfort et al. (2015) aligned cortical maps via optimal transport. More recently, Wang et al. (2015) established an individualized functional network parcellation strategy that may provide landmarks of functional networks for cross-subject alignment. Robinson et al. (2014) proposed a surface based multi-modal alignment technique, which allows for anatomical and local functional features to drive cortical alignment. Here we de-couple anatomy and function, and use the distributed connectivity structure represented in a spectral embedding space as a basis for alignment, and investigate how anatomical- and functional alignment differ.

### *Contribution*

Here, we describe diffeomorphic alignment of the cortical surface based on rs-fMRI connectivity characteristics. We tested whether this would improve the accuracy of alignment of functionally similar regions identified on t-fMRI, by evaluating the overlap of homologous regions mapped across subjects and evaluating group-level task activation analysis. The proposed alignment improved overlap and group-level analysis. Aligning repeat rs-fMRI scans of the same individuals showed that the method is stable, while still detecting displacements across subjects. Further investigation of this anatomo-functional dissociation revealed that it was unevenly distributed across the cortex. To test whether this might be a feasible technique with which to study differences between cohorts, we evaluated the difference between left- and right-handed subjects. Results from the experiments support a strong link between functional resting state and task responses, and that functional alignment with resting state networks improve the group analysis of t-fMRI.

## Diffeomorphic functional surface alignment

We briefly review diffusion map embedding for the representation of the rs-fMRI data, then explain the alignment of individual subject maps in the embedding space, and, finally, detail how this joint embedding map can drive a diffeomorphic alignment of the cortical surface. An illustrative overview of the method is displayed in Fig. 1.

### *Embedding map representation of functional connectivity*

We review embedding of signal correlation patterns by diffusion maps (Coifman and Lafon, 2006) subsequent to the embedding map alignment described in (Langs et al., 2010, 2011).

For each of $S$ subjects, rs-fMRI data $\mathbf{I}^s \in \mathbb{R}^{T\times N}$ consists of $N$ surface nodes $\mathbf{V}$ with a BOLD signal observed at $T$ time points. The connectivity structure of the resting state data can be viewed as a graph, where the vertices represent the surface nodes, and a similarity measure between the corresponding signal time courses defines the edges. We define the edges of this graph as an affinity matrix, $\mathbf{W}^s$, where $\mathbf{W}^s_{ij}$ is the Pearson correlation coefficient between the time-series of nodes $i$ and $j$ in subject $s$, and we keep only the connections with a correlation of $r > 0.25$ to discard weak and negative connections. Subsequently, the graph is checked to ensure that it is a connected graph.

The spectral representation of the functional connectivity structure in each subject is based on a transition probability graph $\mathbf{P}^s$, with $\mathbf{P} = \mathbf{D}^{-\alpha}\mathbf{W}\mathbf{D}^{-\alpha}$. $\mathbf{D}$ is the diagonal matrix of node degrees, i.e.,