Functional Inter-Subject Alignment Outperforms Anatomical Alignment on fMRI Data in Inter-Subject Information Transfer

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Abstract

Group-level analysis in neuroscience requires precise alignment of neural data across participants. A common approach is to spatially align brains and use spatial smoothing to enhance inter-individual overlap. However, this purely anatomical approach makes strong assumptions about functional-anatomical coupling that are likely violated due to substantial inter-individual variability in functional neuroanatomical organization.

In this work, we compare multiple methods which aim to find a common representation of functional magnetic resonance imaging (fMRI) data across participants. The data was recorded from 30 participants listening to naturalistic auditory stimuli (Forrest Gump audio movie). We compare the standard anatomical approach (MNI space combined with spatial smoothing) and three inter-subject alignment methods (multiset canonical correlation analysis (MCCA), Kettenring 1971; group ICA, Calhoun 2009; Hyperalignment, Xu 2012) which seek to find a functional alignment by maximizing similarity of activation time-series between subjects in a latent space under different constraints.

In order to evaluate the inter-subject information transfer of the different alignment methods, we designed a classification task based on decoding the occurrence of function versus content words in the audio movie. Inter-subject classifiers were trained on the aligned data from one set of subjects and tested on a held-out subject in a leave-one-subject-out fashion.

The results show that functional inter- subject alignment methods (accuracy: MCCA, 0.638; ICA, 0.637; Hyperalignment, 0.611; chance level 0.5) greatly outperform the standard anatomical alignment method (MNI space, 0.508). This indicates that the important features for across subject generalization lie within the latent functional spaces, while anatomical-functional representations can be idiosyncratic.

Our work demonstrates that functional inter-subject alignment has the potential to improve the generalizability of data representations when combining data of different subjects.

Introduction

Current approaches to inter-subject alignment of neural recordings primarily rely on spatial registration techniques combined with smoothing to enhance inter-individual correspondence. These include anatomical normalization pipelines for fMRI (e.g., SPM, MNI space) and sensor-level alignment methods for EEG/MEG (e.g., 10/20 system, signal space separation). While these neuroimaging standards fundamentally assume consistent structure-function relationships across individuals, emerging evidence from functional neuroanatomy (Uylings et al., 2005), univariate (Unni et al., 2016), and multivariate analyses (Boos et al., 2021) demonstrates that such anatomical alignment provides only coarse approximations of functional topography.

Therefore, we aim to show that functional inter-subject alignment performs better than anatomical alignment. We do this by setting up an inter-subject decoding task to evaluate the generalization capabilities of data representations found by different alignment methods. Furthermore, we extend previous local approaches, which restricted alignment to local brain patches, to whole-brain alignment.

Methods

Thirty right-handed native German speakers (20–32 years; cognitive/auditory screening confirmed) underwent fMRI while listening to the German-dubbed audio of Forrest Gump. Stimuli included dynamic auditory elements (dialogues, environmental sounds) and audio descriptions.

Functional MRI data were acquired on a 3T Siemens Prisma scanner using multiband EPI (TR=850 ms, 2.5 mm^3 voxels). High-resolution T1-weighted structural images and field maps were collected for anatomical reference and distortion correction. Preprocessing via fMRIPrep included motion correction, slice-timing adjustment, spatial normalization to MNI152NLin6Asym space (2 mm^3 resolution), and nuisance regression (motion parameters, WM/CSF signals). A study-specific gray matter mask restricted analyses to cortical/subcortical regions.

Speech annotations from the studyforrest dataset (Häusler and Hanke, 2021) were used to classify words into two categories: content (nouns, verbs, etc) and function (articles, conjunctions, etc). Temporal boundaries of words were convolved with a hemodynamic response function (HRF) to generate per-volume labels. These labels served as targets in a cross-subject decoding task evaluating functional alignment methods.

Results

To address the high dimensionality of whole-brain gray matter data (117,784 voxels), we first applied principal component analysis (PCA) to each participant's data, reducing the feature space to 800 principal components (PCs). Functional alignment was done in this PC space. MCCA and group ICA further reduced the 800 PCs to 700 components, using a second group-level PCA (MCCA) or ICA (group ICA) on the data of all subjects concatenated along the PC axis.

Both methods were evaluated using a leave-one-subject-out cross-validation framework, where the computation of the shared component space and classifier training excluded the held-out subject. The held-out subject's data was projected into the shared space via linear regression prior to classifier testing.

Hyperalignment followed a distinct validation protocol: the shared template space was computed using all but the held-out subject, and a Procrustes transform mapped the held-out subject's data into this template for classifier evaluation.

For anatomical alignment classifiers were trained and tested directly in the 800-dimensional PC space using the same leave-one-subject-out scheme.

All functional alignment methods significantly outperformed anatomical alignment (mean decoding accuracy 0.508), which was barely above chance (0.5). Mean decoding accuracies for classifying function versus content words were MCCA: 0.638, group ICA: 0.637, and Hyperalignment: 0.611.

Discussion

Our findings demonstrate that functional alignment methods better capture inter-subject neural patterns critical for generalization, whereas anatomical alignment fails to account for functional neuroanatomical variability. Furthermore, we show that functional inter-subject alignment can be done on whole-brain data.

A key limitation of functional alignment as implemented here lies in its dependence on time-synchronized stimuli across participants. The requirement for identical stimulus timing restricts applicability to paradigms with fixed, reproducible stimuli and complicates integration of datasets with variable task designs or naturalistic timing. Advances in stimulus-agnostic alignment—potentially leveraging resting-state functional connectivity or cross-modal latent spaces—could broaden utility.

The practical implications of functional alignment are multifaceted. First, it enables robust aggregation of neuroimaging datasets across studies, even with anatomical variability, enhancing statistical power for rare populations or multi-site collaborations. Second, these methods could accelerate brain-computer interface calibration by "warm-starting" decoders with shared functional templates, reducing user-specific training time. Finally, projecting data into anonymized latent functional spaces—stripped of identifiable anatomical features—offers a privacy-preserving alternative for data sharing, aligning with emerging ethical standards in open neuroscience.

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