Harmonizing Resting-state Functional MRI Data to Increase Sample Size and to Classify Tinnitus Brain Connectivity

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Abstract

The neuroscientific understanding of tinnitus, or ringing in the ears, is limited at present, partly due to a lack of sufficient neuroimaging data. However, data scarcity can be overcome with 'harmonization' methods if scans from independent sites and studies are pooled successfully. We achieved data harmonization by merging a modest tinnitus fMRI dataset acquired in our lab (n=35) with another large dataset, the Lifespan Human Connectome Project Aging (n=377). We measured resting-state functional connectivity (FC) between brain regions, and used deep learning architecture to purge dataset-identifying information from FC maps while retaining characteristic patterns of tinnitus-related FC. Hallmark artifactual information of the datasets was significantly reduced while reconstructing individual FC data. Default mode network connectivity was identified to be crucial for distinguishing tinnitus, as masking the network's connections severely impacted downstream classification on reconstructed FC. The data harmonization model was successful in merging FC matrices from independently acquired fMRI datasets, without losing out on meaningful functional connectivity patterns of interest for the neuropsychological disorder.

Keywords: data harmonization; artificial neural network; deep learning autoencoder; tinnitus; neuropsychological disorder; functional connectivity; resting-state fMRI;

Introduction

It is agreed upon that data sharing can be resourceful for advancing neuroimaging based research, especially for auditory cognitive disorders (Eckert et al., 2023). The debilitating condition of tinnitus is one such hearing disorder that is known to cause psychological, cognitive, and sleep issues (Hall et al., 2018; Langguth et al., 2011; Watts et al., 2018); yet the associated neural bases remain under-studied and also under-funded (compared to other neurological diseases such as dementia). Hence, a useful innovation is to leverage open access databases for benchmarking brain health conditions. A primary issue in combining MRI datasets is the dataset-intrinsic noise owing to differences in scanner types, acquisition parameters, and samples of subjects. In our study, we implemented goal-directed data harmonization on functional connectivity (FC) data (An et al., 2022, Moyer et al., 2020). We pooled together resting-state fMRI FC from Human Connectome Project Aging (HCA; Bookheimer et al., 2019), and our in-house data of tinnitus patients and healthy controls (Lab database). We tested whether the two independent datasets can be harmonized, honoring our broader goal of characterizing tinnitus-related brain connectivity. Our harmonization framework not only removed dataset differences, but also discerned meaningful brain FC patterns for the disorder of tinnitus.

Harmonization of independent fMRI functional connectivity data

Participant matching. Lab dataset included tinnitus (n=15) and control (n=20) groups (43.1±10.8 years, 43% male). From the HCA dataset, we chose 377 subjects that matched in age and gender with at least one of the Lab participants. Individual FC matrices were calculated using pearson's correlation coefficient between 100 brain regions (ROIs) based on Schaefer atlas (Schaefer et al., 2018).

Harmonization framework. The crux of the model was a variational autoencoder (VAE) that mapped the original FC to reconstructed FC utilizing a mean squared error (MSE). A logistic regression model was pre-trained to identify source dataset (HCA/Lab) from original FC, and the prediction function was included as a loss term in VAE. A feed-forward tinnitus classifier network was trained concurrently with the VAE utilizing a binary cross-entropy loss, which was also used to tune the VAE weights (Figure 1).

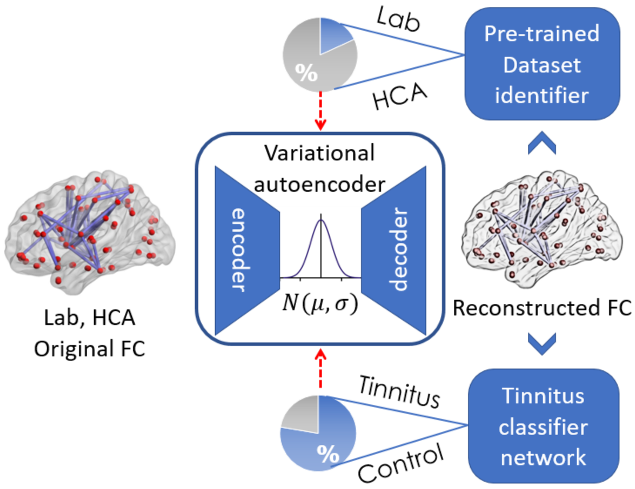

Figure 1: FC harmonization framework. Dashed red lines depict additional error terms in VAE cost function.

Dataset classifier was pre-trained, in repetitions, with bootstrapped train and test FC data drawn from Lab controls and their matched HCA subjects. Using the averaged model coefficients for predicting the dataset correctly classified 100% of all Lab controls FC and 93.35% of HCA FC. The cost function of VAE included a 'dataset identifiability' measure, $|0.5 - p_{dataset}|$, where $p_{dataset}$ was the predicted probability of the dataset classifier on reconstructed FC.

The VAE and the tinnitus classifier were trained in unison for 500 epochs, with train/test datapoints for tinnitus chosen from Lab data, and controls from both Lab and HCA-matched data. The quality of FC reconstruction improved over training epochs, as evidenced by decreasing MSE error in both the train and test data as well as across the independent training repetitions. During training, the reconstructed FC output by VAE was used as input to the tinnitus classifier. After training phase completion, reconstructed FC showed more accurate category predictions (median predicted probability increased for tinnitus category, and decreased for control; Figure 2 lighter plots). Tinnitus classifier, which was trained on reconstructed FC, showed poorer category predictions on the original FC ($p<0.001$; Figure 2 darker plots). This suggests that the harmonized version of FC retained or enhanced statistical patterns among tinnitus-identifying functional connections, which may not manifest as evidently in the unharmonized counterpart.

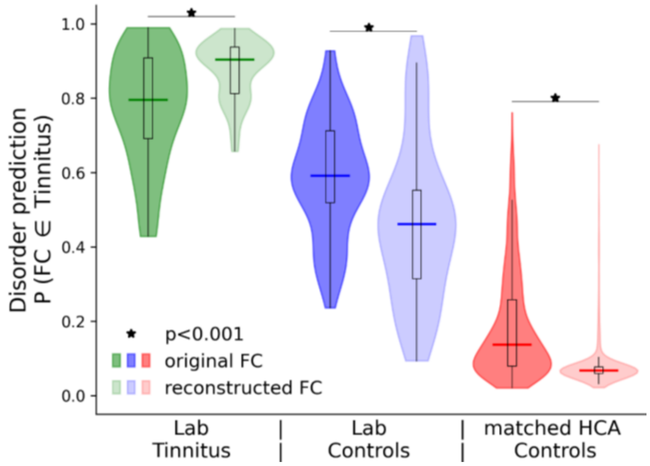

Figure 2: FC Tinnitus classification before (original) and after (reconstructed) goal-directed harmonization

Next, we investigated whether tinnitus detection was driven by meaningful network connections, or by possible artifactual patterns in VAE-reconstructed FC. We evaluated tinnitus classifier prediction after occluding the FC edges for one functional network (Yeo et al., 2011) at a time by setting their input layer weights to zero. Interestingly, masking default mode network (DMN) connectivity alone lead to the greatest reduction in classification accuracy (~70% decrease in median probability compared to full FC).

Conclusion

We implemented an interconnected arrangement of neural networks to harmonize data from a small tinnitus fMRI dataset, and a separately acquired large dataset of healthy subjects. This addressed the cognitively relevant problem of differentiating brain interaction patterns associated with a neurological condition. Harmonized FC identified DMN connectivity as most crucial in distinguishing tinnitus, corroborating previous results on individuals with chronic tinnitus and varying degrees of severity and habituation (Rosemann & Rauschecker, 2023; Schmidt et al., 2013, 2017).

Acknowledgement

This work was supported by the Defense Health Agency [Award ID: W81XWH-15-2-0032], the Discovery Partners Institute, the National Center for Supercomputing Applications Illinois Computes program, the Nadine Barrie Smith Memorial Fellowship (granted to S.A.), and the Beckman Graduate Fellowship (granted to S.A.).

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