Paper: Resting State Network Estimation in Individual Subjects

Hacker, Carl D., Timothy O. Laumann, Nicholas P. Szrama, Antonello Baldassarre, Abraham Z. Snyder, Eric C. Leuthardt, and Maurizio Corbetta. "Resting state network estimation in individual subjects." Neuroimage 82 (2013): 616-633.

Advanced Computer Integrated Surgery II Literature Review

Group 9: Arden Chew

Mentors: Dr. Haris Sair and Dr. Mathias Unberath

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Personal Project Summary

Resting state functional magnetic resonance imaging (rsfMRI) provides valuable insight into the brain's functional organization, however labeling network components and organizing them into the correct hierarchical structure remains a challenge. My project looks to automate the hierarchical organizing and labeling of rsfMRI networks components for diagnostics and preoperative care.

Selection Motivation

In this paper, Hacker sought to solve the same fundamental problem as I aim to with my project: to computationally label rsfMRI network components. While the paper takes a more rudimentary approach and simplified learning model, it is the first and only paper to successfully implement a resting state specific fMRI network component labeling algorithm. By reading this paper I aimed to better understand data processing techniques with rsfMRI data, learn from and critique network architecture choices and justification, build on the framework they have laid out for medical application based rsfMRI brain component labeling, and evaluate fMRI accuracy testing procedure.

Summary and Background

Given that this paper was published in 2013, it is necessary to note that the state of clinical applicability for rsfMRI was still in its early beginnings. The signal processing and classification method space therefore was severely limited. Hacker's work in this paper, as well as subsequent work with Washington University, successfully paved the way for future endeavors in computational applications of rsfMRI data science.

The paper's stated objective is to reliably classify rsfMRI scans of healthy individuals into seven pre-selected brain networks. To achieve said objective the following general workflow of rsfMRI classification model training was employed: 1) rsfMRI pre-processing and signal normalization; 2) voxel-wise correlation map generation from pre-selected regions of interest; 3) principal component analysis dimensionality reduction; 4) multi-layer perceptron feed forward eigenvector training.

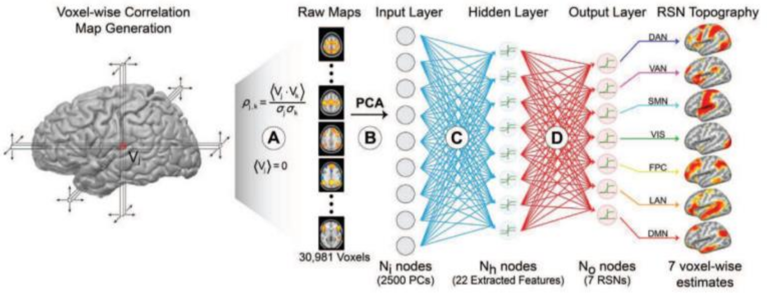


Figure 1: Hacker et al. Primary voxel-wise network architecture and data flow.

The resulting average validation accuracy of their network model after hyper-parameter tuning was 97.7% with 0.85% standard deviation, and 19.4% RMS error, indicating strong success.

Significance

This paper is most significant for its role as the first rsfMRI automated classification work. Not only does the work provide a basis for many techniques in rsfMRI application now, but it also evaluates the limitations of its own model, and contrasts with previously existing techniques for task-based fMRI. Hacker's high validation accuracies across a range of tests validate that these methods have potential for clinical grade application once improved in granularity. Furthermore, Hacker's pre-processing techniques of PCA gave rise to rsfMRI component-based separation. While PCA is no longer primarily used in rsfMRI analysis, the current standard of independent component analysis (ICA) was adopted after recognition of PCA's initial success in the field. Lastly, this paper notes the significance of addressing the hierarchical structure of rsfMRI network topology. While the preselected PCA approach to semi-hierarchical feature learning was incomplete in the paper, it does well to address the limitations of the paper, and the subsequent capabilities needed for clinical use. In my project I primarily aim to address this issue of hierarchical structure analysis with an unsupervised methodology.

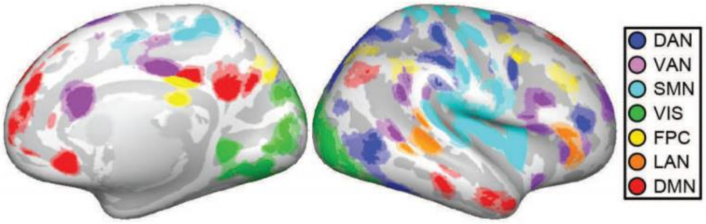
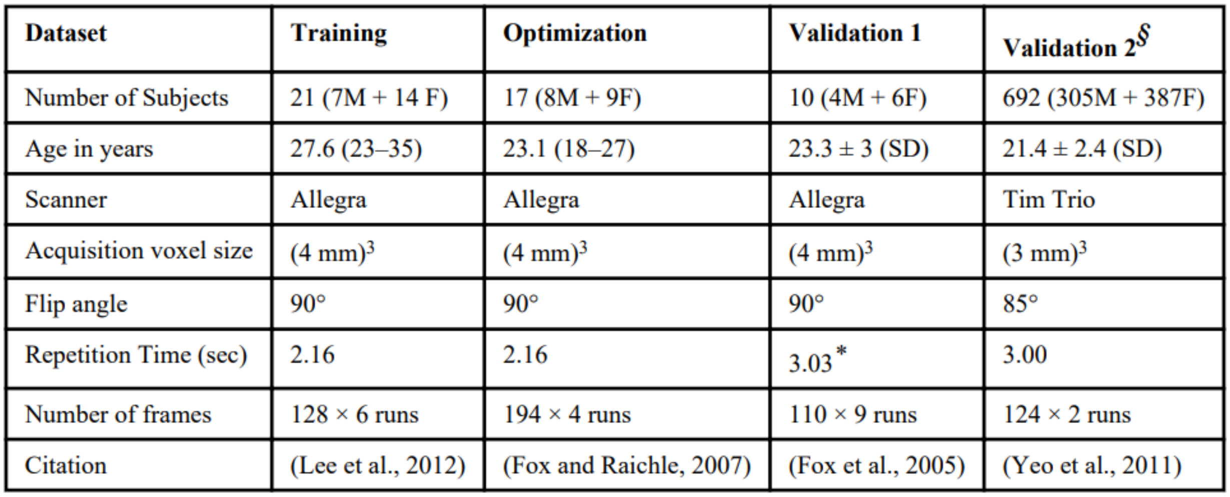


Figure 2: Hacker et al. Pre-selected brain network components pertaining to existing partial hierarchical topology.

Technical Methods

Data acquisition

Separate rsfMRI scan datasets were acquired for training, optimization, validation, and testing. Note that the testing dataset is called validation 2, while validation 1 corresponds to a typical validation set. For training, optimization, and validation (1), 48 young and healthy adults were scanned at Washington University School of Medicine's Neuroimaging Laboratories (NIL). Imaging for these 48 subjects was conducted with a 3T Allegra MRI scanner. Conversely, 692 subjects were scanned with a Tim Trio MRI scanner as part of the Harvard-MGH Brain Genomics Superstruct Project. These 692 scans were reserved for testing.



Dataset	Training	Optimization	Validation 1	Validation 2§
Number of Subjects	21 (7M + 14 F)	17 (8M + 9F)	10 (4M + 6F)	692 (305M + 387F)
Age in years	27.6 (23–35)	23.1 (18–27)	23.3 ± 3 (SD)	21.4 ± 2.4 (SD)
Scanner	Allegra	Allegra	Allegra	Tim Trio
Acquisition voxel size	$(4\ \mathrm{mm})^3$	$(4\ \mathrm{mm})^3$	$(4\ \mathrm{mm})^3$	$(3\ \mathrm{mm})^3$
Flip angle	90°	90°	90°	85°
Repetition Time (sec)	2.16	2.16	3.03*	3.00
Number of frames	128 × 6 runs	194 × 4 runs	110 × 9 runs	124 × 2 runs
Citation	(Lee et al., 2012)	(Fox and Raichle, 2007)	(Fox et al., 2005)	(Yeo et al., 2011)

Figure 3: Hacker et al. Dataset selection and parameters.

Neuroimaging preprocessing

Normalization of rsfMRI scans temporally, spatially, and regionally is necessary in all resting state comparative network topology studies. Hacker employs the standard suite of rsfMRI normalization techniques including “compensation for slice-dependent time shifts, elimination of systematic odd-even slice intensity differences due to interleaved acquisition, and rigid body correction of head movement within and across runs.” In addition, gaussian spatial smoothing was employed on the resultant normalized volumetric data.

For visualization purposes, Hacker employed Harvard’s existing FreeSurfer platform for cortical reconstruction and volume segmentation. This allowed for the creation of a grey matter mask by which BOLD signal enabled fMRI networks could be projected onto.

Network architecture and design choices

The first layer of the network architecture takes the normalized rsfMRI volumetric scans and runs principal component analysis to identify 2,500 components (eigenvectors). The 2,500 component number was determined as a hyper-parameter of the network after validation adjustment. Each principal component was subsequently fed into corresponding perceptron forming a 2,500 node input layer. Following the input layer was a densely sampled 22 layer feed forward network producing an 8 class label. 7 of these output classes corresponded to preselected hierarchical network components, while the last was reserved for noise components.

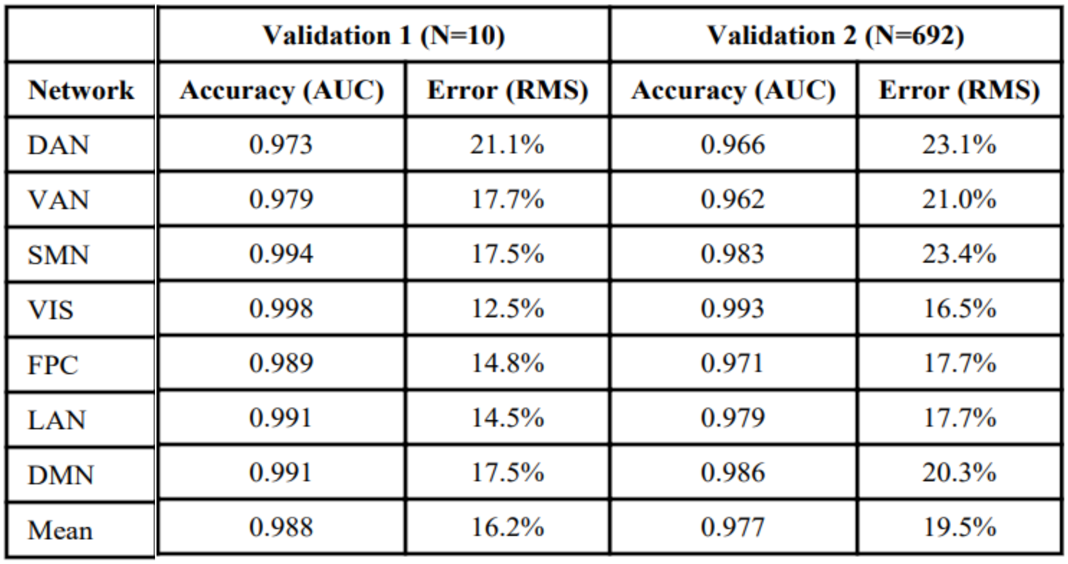
Hyper-parameter tuning was conducted solely with the reserved optimization dataset, while network tuning relied on the validation 1 dataset. Hacker settled upon usage of simulated annealing optimization and cross entropy loss. Early stopping was the primary methodology of regularization.

Testing

Firstly, individual variability was study through validation testing in the validation 1 dataset. Since this dataset retains the hospital and scanning properties of the training dataset, network architecture choices could reliably be re-evaluated from this testing strategy. Validation at the group level was conducted on the separate Harvard dataset comprising validation 2. For both testing techniques, the same standard normalization preprocessing was performed and PCA transformed the volumetric data into viable network inputs.

Results

Mean accuracy on the tuned Validation 1 dataset accrued a score of 98.8% with a 16.2% root mean squared (RMS) error. Mean accuracy for the group study in Validation 2 dataset scored 97.7% accuracy with 19.5% RMS error. Network component specific test results are available below.



	Validation 1 (N=10)		**Validation 2 (N=692)**	
Network	**Accuracy (AUC)**	**Error (RMS)**	**Accuracy (AUC)**	**Error (RMS)**
DAN	0.973	21.1%	0.966	23.1%
VAN	0.979	17.7%	0.962	21.0%
SMN	0.994	17.5%	0.983	23.4%
VIS	0.998	12.5%	0.993	16.5%
FPC	0.989	14.8%	0.971	17.7%
LAN	0.991	14.5%	0.979	17.7%
DMN	0.991	17.5%	0.986	20.3%
Mean	0.988	16.2%	0.977	19.5%

Figure 4: Hacker et al. Reported validation accuracies.

Personal Critique

Places for improvement

<u>Semi-hierarchical model</u>: While the paper successfully recognizes that resting state network components retain a hierarchical topology, it fails to provide a viable automated solution to hierarchical structure recognition. Instead, Hacker opts for preselecting network components with membership in a well known hierarchical order. Not only does this preselected semi-

hierarchical model fail to recognize topological organization in automation, but it also does not incorporate the topological relations into its label classification.

PCA: While applications of ICA were relatively spars in 2013 while the paper was written, PCA offers a few glaring downfalls which the author does not account for. Most notably, PCA is incapable of differentiating independent temporal signals by which resting state components tend to define themselves. Instead, an enormously large number of principal components (eigenvectors) are fed into the feedforward deep network for brain component approximation. This network is therefore inherently correlated by a preset method which does not correlate to any neurological structure. In addition, the number of PCA components selected for input usage was chosen manually. This manual selection defeats a portion of the automation capability while also requiring a computational expert to replicate such a tool on new datasets.

Regularization: The only regularization strategy noted in the paper is early stopping, however early stopping tuning also requires a computational expert and many training iterations. Furthermore, training repeatability across future datasets would be limited by the early stopping parameter. Instead network dropout could provide a more robust and repeatable regularization strategy. In addition, dropout would mitigate potentially undiagnosed vanishing gradient issues within such a deep network architecture.

Training data selection: This paper has two major faults in its training data selection. Firstly, the paper only trains using scans from a single scanning machine within a single hospital. Existing hospital and machine biases can prevent the model from generalizing well. Secondly, the paper trains exclusively on healthy patients. As a clinical tool, something that operates successfully only on already healthy patients is not particularly useful.

Highlights

Novelty: Though it is easy to critique a paper after nearly a decade of development in the field, the reality is that this paper was groundbreaking for rsfMRI classification. The scope of methods explored was minimal and yet Hacker manages to make insightful network choices, and successfully identifies confounding variables in the study. Moreover, as a validation study, the high testing accuracy achieved and usage of novel automation techniques provides much to build on.

Algebraic comparison of similar models: While Hacker highlights the usage of a multi-layer network (MLN) in the study, a thorough algebraic justification of the advantages of an MLN over both dual regression and linear discriminant analysis is also provided. This is particularly thoughtful, especially considering the future work that sought to improve on this paper.

Neurological motivation recognition: The paper successfully recognizes the neurological confounding variables of the 7 pre-selected brain components and applies this understanding to pointed hyper-parameter and network tuning. This is specifically evident in the case by case validation 1 study and subsequent adjustments made to address neurological correlations. Furthermore, significance testing was conducted to indicate that validation accuracies for each individual component are not entirely based on successes in neighboring components.

Personal Takeaways

- Learned standard methodologies for rsfMRI preprocessing which I can apply in my own data processing scripts
- An improved understanding of network topologies, and the pitfalls of brain network correlations to be aware of
- Learned new methods of individual validation testing rather than exclusively group testing
- A holistic understanding of how rsfMRI volumes interact with deep networks

Reference

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