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Identifying HIV Associated Neurocognitive Disorder Using Large-Scale Granger Causality Analysis on Resting-State Functional MRI

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Abstract

We investigate the applicability of large-scale Granger Causality (lsGC) for extracting a measure of multivariate information flow between pairs of regional brain activities from resting-state functional MRI (fMRI) and test the effectiveness of these measures for predicting a disease state. Such pairwise multivariate measures of interaction provide high-dimensional representations of connectivity profiles for each subject and are used in a machine learning task to distinguish between healthy controls and individuals presenting with symptoms of HIV Associated Neurocognitive Disorder (HAND). Cognitive impairment in several domains can occur as a result of HIV infection of the central nervous system. The current paradigm for assessing such impairment is through neuropsychological testing. With fMRI data analysis, we aim at non-invasively capturing differences in brain connectivity patterns between healthy subjects and subjects presenting with symptoms of HAND. To classify the extracted interaction patterns among brain regions, we use a prototype-based learning algorithm called Generalized Matrix Learning Vector Quantization (GMLVQ). Our approach to characterize connectivity using lsGC followed by GMLVQ for subsequent classification yields good prediction results with an accuracy of 87% and an area under the ROC curve (AUC) of up to 0.90. We obtain a statistically significant improvement ($p < 0.01$) over a conventional Granger causality approach (accuracy = 0.76, AUC = 0.74). High accuracy and AUC values using our multivariate method to connectivity analysis suggests that our approach is able to better capture changes in interaction patterns between different brain regions when compared to conventional Granger causality analysis known from the literature.

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Keywords

Resting-state fMRI; functional connectivity; Granger causality; multi-voxel pattern analysis; vector quantization; HIV; neurological disorders; HIV Associated Neurocognitive Disorder (HAND)

1. INTRODUCTION

Patients living with Human Immunodeficiency Virus (HIV) infection are susceptible to develop symptoms of HIV Associated Neurocognitive Disorder (HAND) as a result of the virus entering the central nervous system. The impact on the cognitive abilities of a patient is assessed using neuropsychological tests, which are often subjective and cannot be used to diagnose early infection of the brain before symptoms manifest. In this analysis, we investigate the presence of HAND by studying the ability of multivariate resting-state fMRI analysis to recognize differences in interaction patterns among different brain regions with the end goal of developing a framework to characterize disease progression more objectively. To this end, we study changes of patterns in resting-state brain activity to reveal differences between diseased and healthy subjects. Previous studies have used a framework, referred to as Multi-voxel Pattern Analysis (MVPA) [1], which extracts patterns from the functional connectivity profiles of subjects with and without a neurological disease, such as major depression [2]. Conventionally, such studies use cross-correlation to obtain functional connectivity profiles for every subject. In this work, we study the use of large-scale Granger causality (lsGC) [3] analysis to extract such profiles.

Large-scale Granger causality [3] was developed to circumvent the ill-posed problem faced by traditional conditional Granger causality analysis (cGC) [4] while trying to obtain a voxel-wise measure of multivariate causal interaction. The ill-posed problem arises because the number of recorded voxels is much larger than the number of volumes of the brain recorded, i.e. the length of the voxel time-series. In this study, although we don't encounter this problem since we perform a region-wise time-series analysis, we demonstrate the usability and effectiveness of lsGC over cGC for conditions where an ill-posed problem is not faced. This is demonstrated by examining lsGC model parameters that gives it an edge over cGC. To this end, we investigate the effectiveness of lsGC, under different parameter settings, to extract connectivity profiles, following which MVPA is performed to distinguish between healthy individuals and individuals presenting with symptoms of HIV Associated Neurocognitive Disorder (HAND). We carry out MVPA using Generalized Matrix Learning Vector Quantization (GMLVQ) [5], which is a prototype-based learning algorithm that can handle high-dimensional discriminative tasks without requiring an explicit feature extraction step prior to classification. Furthermore, we also compare how lsGC performs against traditional cGC [4]. This work is embedded in our group's endeavor to expedite 'big data' analysis in biomedical imaging by means of advanced machine learning and pattern recognition methods for computational radiology and radiomics, e.g. [6–36].

2. DATA

2.1 Functional MRI data

Functional MRI (fMRI) scans from 29 subjects (14 with symptoms of HAND and 15 healthy controls) were acquired at the Rochester Center for Brain Imaging (Rochester, NY, USA) using a 3T MRI scanner. The cohort consisted of subjects aged 32–53 years. The resting-state fMRI scan parameters were: Echo time (TE) = 23 ms, repetition time (TR) = 1650 ms, flip angle (FA) = 84°, 96 × 96 acquisition matrix. A total of 250 temporal scan volumes with 25 slices at a slice distance of 5 mm were acquired from each subject. High-resolution structural T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scans were used to co-register the functional sequences to the standard MNI152 template [37]. The MPRAGE sequence parameters were as follows: TR = 2530 ms, TE = 3.44 ms, isotropic voxel size 1mm, FA = 7°, acquisition time ~ 3 minutes. Written consent was given by the scanned individuals according to an IRB-approved study protocol.

To correct for motion during scan, for interleaved acquisition, and to extract the brain, the fMRI data was processed using the FMRIB's Software Library (FSL version 5.0) [38]. The MNI152 template was used to register the data to a standardized brain atlas space, and removal of the whole brain time-series was done using a nuisance regressor. In addition, high-pass filtering was performed to remove signal drifts, and the first 10 volumes temporal scan volumes were discarded to eliminate initial saturation effects. The voxel time-series were normalized to unit standard deviation and zero mean to focus on signal dynamics rather than amplitude [39]. Finally, the brain activity was represented by 90 regions, where the regions were defined by using the Automated Anatomic Labelling (AAL) template [40]. Each regional time-series was represented by the average time-series of all voxels included in the region.

3. METHODS

3.1 Large-scale Granger causality analysis

We use large-scale Granger causality (lsGC) [3] to obtain a measure of directed multivariate information flow between every pair of regional time-series in the resting-state human brain. The principle of lsGC is derived from that of Granger causality [5, 41], which states that if the prediction quality of time-series $\mathbf{x}_s$ improves in the presence of time-series $\mathbf{x}_r$, then $\mathbf{x}_r$ Granger causes $\mathbf{x}_s$. Large-scale Granger causality comprises of estimating a time point in the future, using vector auto-regressive (VAR) modelling (of order d), in a dimension-reduced space defined by retaining the first c Principal Components (PC) of the time-series ensemble. These predictions are transformed back to the original time-series ensemble space using the inverse of the linear transformation function in the initial rotation of the axes to the PC space. The prediction errors, i.e. residuals, are used to obtain the lsGC coefficients. We calculate the variance of the residuals, when the full ensemble was used for obtaining the PCs, and compare these with those residuals obtained when information of one time-series is removed. We thus obtain a matrix of lsGC coefficients, containing measures of directed multivariate information flow scores for every pair of time series.

Consider an ensemble of time-series $\mathbf{X} \in \mathbb{R}^{N \times T}$, where N and T are the number of time-series and the number of temporal samples respectively. Let $\mathbf{X} = (\mathbf{x}_1, \mathbf{x}_2, \mathbf{x}_3, \dots, \mathbf{x}_N)^T$ be the whole multidimensional system, $\mathbf{x}_n \in \mathbb{R}^T$ a single time-series with $n \in \{1, 2, \dots, N\}$, where $\mathbf{x}_n = (x_n(1), x_n(2), \dots, x_n(T))$. Large-scale Granger causality differs from cGC by performing Granger causality analysis in an embedded lower dimension space. This is carried out by obtaining a multivariate GC score by first decomposing $\mathbf{X}$ into its first c high-variance principal components $\mathbf{Z} \in \mathbb{R}^{c \times T}$ using Principal Component Analysis (PCA), i.e.,

$$\mathbf{Z} = \mathbf{W}\mathbf{X}.$$

Subsequently, $\mathbf{Z}$ is modelled using Vector Auto-Regressive (VAR) modelling of order d and the estimate $\hat{\mathbf{Z}}$ is computed by using the d auto-regression parameter matrices, each of size $c \times c$. To obtain the influence of time-series $\mathbf{x}_r$ on all other time-series, we remove the information of $\mathbf{x}_r$ from the transformation matrix $\mathbf{W}$, obtain $\mathbf{Z}_{\mathbf{x} \setminus \mathbf{x}_r}$ and model $\hat{\mathbf{Z}}_{\mathbf{x} \setminus \mathbf{x}_r}$ as its VAR estimate.

The two estimates $\hat{\mathbf{Z}}$ and $\hat{\mathbf{Z}}_{\mathbf{x} \setminus \mathbf{x}_r}$ are projected into the original high-dimensional space using the respective inverse PCA transformation. Following this, the errors, in the original high dimensional space, $\mathbf{E}$ and $\mathbf{E}_{\mathbf{x} \setminus \mathbf{x}_r}$, are computed after which we quantify the prediction quality by comparing the variance of the prediction errors obtained with and without consideration of $\mathbf{x}_r$. If the variance of the prediction error of a given time series, say $\mathbf{x}_s$, decreases with using $\mathbf{x}_r$, then we say that $\mathbf{x}_r$ Granger-causes $\mathbf{x}_s$ [4].

$$F_{\mathbf{x}_r \rightarrow \mathbf{x}_s} = \ln \frac{\sigma(\mathbf{e}_{\mathbf{x}_s, \mathbf{x} \setminus \mathbf{x}_r})}{\sigma(\mathbf{e}_{\mathbf{x}_s})}$$

$F_{\mathbf{x}_r \rightarrow \mathbf{x}_s}$ is the GC index for the influence of $\mathbf{x}_r$ on $\mathbf{x}_s$, which is stored in the affinity matrix $\mathbf{A}$ at position $\mathbf{A}_{(s, r)}$. $\mathbf{e}_{\mathbf{x}_s, \mathbf{x} \setminus \mathbf{x}_r}$ is the error in predicting $\mathbf{x}_s$, when $\mathbf{x}_r$ was not considered, and $\mathbf{e}_{\mathbf{x}_s}$ is the error when $\mathbf{x}_r$ was used.

To quantitatively evaluate the performance of our lsGC method, we compare this approach to a conditional Granger causality method (referred to as cGC here) [4] from the literature, which does not require any low-dimensional embedding and obtains GC coefficients in the original ensemble space. For cGC, $\mathbf{Z} = \mathbf{X}$ where $\mathbf{W}$ is the identity matrix. However, the need for lsGC becomes relevant, when N and T are very similar or when $N > T$, where N is the size of the ensemble, i.e. the number of time-series, and T is the length of the series. The quantities N and d both increases the number of parameters to be computed, whose estimation is limited by length T . The lsGC method alleviates this problem, as it incorporates a reversible dimension reduction step by decreasing the number of free parameters to be estimated for time-series modelling.

3.2 MVPA - Classification using GMLVQ

Subsequent to obtaining the connectivity profiles, i.e. affinity matrices, from every subject using lsGC and cGC, we symmetrized and vectorized them into high-dimensional feature vectors and use them as input to the Generalized Matrix Learning Vector Quantization (GMLVQ) classifier and test its ability to classify between the two subject groups.

GMLVQ is a prototype-based locally linear distance learning approach, which shows good generalizability for high-dimensional data [5]. The GMLVQ classifier does not require an explicit feature extraction step prior to classification. The classifier was trained with the following restrictions: the training data received equal number of instances from both groups and the independent test set had at least one instance from each group. A 90%/10% training/test separation was used for this study in an iterative cross-validation scheme, where the robustness was validated over 100 iterations of training/test split.

All procedures were implemented using MATLAB 8.4 (MathWorks Inc., Natick, MA, 2014). The MATLAB implementation of GMLVQ was taken from [42]. Wilcoxon signed-rank test was used to test for significant differences between the methods. A flow chart of the steps involved in this analysis is shown in Figure 1.

4. RESULTS

Figure 2 shows the symmetrized connectivity profiles constructed using lsGC and cGC from the fMRI sequence of one of the subjects. These matrices are converted to high-dimensional feature vectors and used for classification between healthy and diseased subjects. We use the Area Under the Receiver Operator Characteristic Curve (AUC) and accuracy of classification to evaluate the ability of both approaches to predict the disease state. An AUC = 1 indicates a perfect classification and AUC = 0.5 indicates random classification.

Figure 3 shows the results obtained when the number c of retained principal components and mean explained variance (EV) are chosen $c = 1$ (EV = 0.52), $c = 2$ (EV = 0.67), and $c = 20$ (EV = 0.96), respectively. The maximum order d that can be used with cGC is 2, before the problem becomes underdetermined. The plot corresponding to cGC (plotted in purple) in Figure 2 represents the result at order $d = 2$ alone. It is plotted in the same figure for easy comparison between lsGC and cGC.

The results in Figure 3 show that, as the number c of retained PCs increase, the classification results initially improve. This would be because the ensemble is better represented with a higher c . However, increasing c to 20 results in a slight decrease in classification performance, because with increasing number c of PCs, the number of parameters to be estimated increases as well. A similar argument may explain why cGC performs poorly when compared to lsGC for EV > 0.60. With cGC even for an order of 2, the number of parameters to be estimated is very large, since $N = 90$, when compared to lsGC that can have $c \ll N$. This also suggests that most of the relevant information required to separate the two cohorts is present in the first few time-series of the ensemble.

5. NEW AND BREAKTHROUGH WORK

We investigate the use of large-scale Granger causality (lsGC) in establishing meaningful connectivity profiles and test its ability to predict a neurological disease state, such as HAND. We compare our approach to cGC, which is a commonly used conditional GC method. However, effectiveness of cGC, is limited by the length of the time-series, i.e. the amount of recorded brain activity, as effective estimation of the VAR model parameters improves with increase in time-series length, i.e. number of samples. The high AUC and accuracy values using lsGC derived feature vectors (connectivity profiles) suggest that lsGC can be more useful than cGC in effectively capturing the disease state of subjects with and without any cognitive impairment as a result of HAND. We also use Generalized Matrix Learning Vector Quantization (GMLVQ) to classify connectivity patterns between the two cohorts. The results indicate that our multivariate directed connectivity analysis approach, lsGC, with embedded dimension reduction permits to predict neurological disease state from fMRI connectivity analysis with high accuracy.

6. CONCLUSION

We present an approach for classifying subjects presenting with HIV Associated Neurocognitive Disorder (HAND) from healthy controls by first establishing a measure of multivariate interaction between different regional brain activities in resting-state fMRI using lsGC. To ensure that every subject is represented by a set of features (connectivity profiles) that represent interactions between the same pair of regions, the data from all the subjects were registered to a standard space and regional time-series were extracted using a standard template.

We then train a classifier to recognize patterns that discriminate between the two subject groups based on such connectivity information, and test its performance in an iterative cross-validation scheme. The high AUC and accuracy values obtained using lsGC demonstrates the applicability of such a multivariate method for effective connectivity analysis in fMRI data. In conclusion, lsGC has potential to provide neuroimaging derived biomarkers and clinically useful information about how the underlying dynamics of the resting human brain differs between healthy subjects and subjects presenting with symptoms of HAND.

This work is not being and has not been submitted for publication or presentation elsewhere.

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References

1. Norman KA, Polyn SM, Detre GJ, Haxby JV. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. *Trends Cognitive Sciences*. 2006; 10:424–430. [PubMed: 16899397]

2. Zeng LL, Shen H, Liu L, Wang L, Li B, Fang P, Zhou Z, Li Y, Hu D. Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain*. 2012; 135(5): 1498–1507. [PubMed: 22418737]
3. D'Souza AM, Abidin AZ, Leistriz L, Wismüller A. Large-scale Granger causality analysis on resting-state functional MRI. *SPIE Medical Imaging, International Society for Optics and Photonics*. 2016:97880L–97880L.
4. Liao W, Mantini D, Zhang Z, Pan Z, Ding J, Gong Q, Yang Y, Chen H. Evaluating the effective connectivity of resting state networks using conditional Granger causality. *Biological Cybernetics*. 2010; 102(1):57–69. [PubMed: 19937337]
5. Schneider P, Biehl M, Hammer B. Adaptive relevance matrices in learning vector quantization. *Neural Computation*. 2009; 21(12):3532–3561. [PubMed: 19764875]
6. Wismüller, A. PhD Thesis. Technical University of Munich, Department of Electrical and Computer Engineering; 2006. Exploratory Morphogenesis (XOM): a novel computational framework for self-organization.
7. Wismüller A, Meyer-Bäse A, Lange O, Auer D, Reiser MF, Sumners D. Model-free functional MRI analysis based on unsupervised clustering. *Journal of Biomedical Informatics*. 2004; 37(1):10–18. [PubMed: 15016382]
8. Wismüller, A., Vietze, F., Dersch, DR. Handbook of medical imaging. Academic Press Inc; 2000. Segmentation with neural networks; p. 107-126.
9. Leinsinger G, Schlossbauer T, Scherr M, Lange O, Reiser M, Wismüller A. Cluster analysis of signal-intensity time course in dynamic breast MRI: does unsupervised vector quantization help to evaluate small mammographic lesions? *European radiology*. 2006; 16(5):1138–1146. [PubMed: 16418862]
10. Wismüller A, Vietze F, Behrends J, Meyer-Bäse A, Reiser M, Ritter H. Fully automated biomedical image segmentation by self-organized model adaptation. *Neural Networks*. 2004; 17(8):1327–1344. [PubMed: 15555869]
11. Twellmann, T., Saalbach, A., Muller, C., Nattkemper, TW., Wismuller, A. Detection of suspicious lesions in dynamic contrast enhanced MRI data. *Engineering in Medicine and Biology Society, 2004. IEMBS'04. 26th Annual International Conference of the IEEE; Sep. 2004 p. 454-457.*
12. Schlossbauer T, Leinsinger G, Wismuller A, Lange O, Scherr M, Meyer-Bäse A, Reiser M. Classification of small contrast enhancing breast lesions in dynamic magnetic resonance imaging using a combination of morphological criteria and dynamic analysis based on unsupervised vector-quantization. *Investigative radiology*. 2008; 43(1):56. [PubMed: 18097278]
13. Varini, C., Nattkemper, TW., Degenhard, A., Wismuller, A. Breast MRI data analysis by LLE. *Neural Networks, Proceedings. 2004 IEEE International Joint Conference on 3; Jul. 2004 p. 2449-2454.*
14. Hoole P, Wismüller A, Leinsinger G, Kroos C, Geumann A, Inoue M. Analysis of tongue configuration in multi-speaker, multi-volume MRI data. *Proc 5th Semin Speech Prod Model Data CREST Work Model Speech Prod Mot Plan Articul Model*. 2000:157–160.
15. Wismüller, A., Dersch, DR., Lipinski, B., Hahn, K., Auer, D. ICANN 98. Springer; London: 1998. A neural network approach to functional MRI pattern analysis—clustering of time-series by hierarchical vector quantization; p. 857-862.
16. Wismüller, A., Vietze, F., Dersch, DR., Behrends, J., Hahn, K., Ritter, H. *Neurocomputing*. Vol. 48. Elsevier; 2002. The deformable feature map—a novel neurocomputing algorithm for adaptive plasticity in pattern analysis; p. 107-139.
17. Behrends, J., Hoole, P., Leinsinger, GL., Tillmann, HG., Hahn, K., Reiser, M., Wismüller, A. *Bildverarbeitung für die Medizin 2003*. Springer; Berlin, Heidelberg: 2003. A segmentation and analysis method for MRI data of the human vocal tract; p. 186-190.
18. Wismüller A, Dersch DR. Neural network computation in biomedical research: chances for conceptual cross-fertilization. *Theory in Biosciences*. 1997; 116(3):229–240.
19. Bunte K, Hammer B, Villmann T, Biehl M, Wismüller A. Exploratory Observation Machine (XOM) with Kullback-Leibler Divergence for Dimensionality Reduction and Visualization. *ESANN*. 2010; 10:87–92.

20. Wismüller, A., Vietze, F., Dersch, DR., Hahn, K., Ritter, H. ICANN 98. Springer; London: 1998. The deformable feature map—adaptive plasticity for function approximation; p. 123-128.
21. Wismüller, A. Advances in Self-Organizing Maps. Springer; Berlin Heidelberg: 2009. The exploration machine—a novel method for data visualization; p. 344-352.
22. Wismüller, A. Method, data processing device and computer program product for processing data. US Patent. 7,567,889. 2009.
23. Meyer-Bäse, A., Jancke, K., Wismüller, A., Foo, S., Martinetz, T. Eng Appl Artif Intell. Vol. 18. Elsevier; 2005. Medical image compression using topology-preserving neural networks; p. 383-392.
24. Huber, MB., Nagarajan, M., Leinsinger, G., Ray, LA., Wismüller, A. SPIE Med Imaging. Vol. 7624. International Society for Optics and Photonics; 2010. Classification of interstitial lung disease patterns with topological texture features; p. 762410
25. Wismüller A. The exploration machine: a novel method for analyzing high-dimensional data in computer-aided diagnosis. SPIE Med Imaging. 2009:72600G–72600G.
26. Bunte, K., Hammer, B., Villmann, T., Biehl, M., Wismüller, A. Neurocomputing. Vol. 74. Elsevier; 2011. Neighbor embedding XOM for dimension reduction and visualization; p. 1340-1350.
27. Wismüller, A. Advances in Self-Organizing Maps. Springer; Berlin Heidelberg: 2009. A computational framework for nonlinear dimensionality reduction and clustering; p. 334-343.
28. Huber, MB., Nagarajan, MB., Leinsinger, G., Eibel, R., Ray, LA., Wismüller, A. Med Phys. Vol. 38. American Association of Physicists in Medicine; 2011. Performance of topological texture features to classify fibrotic interstitial lung disease patterns; p. 2035-2044.
29. Wismüller A, Verleysen M, Aupetit M, Lee JA. Recent Advances in Nonlinear Dimensionality Reduction, Manifold and Topological Learning. ESANN. 2010
30. Wismüller, A., Meyer-Bäse, A., Lange, O., Reiser, MF., Leinsinger, G. Med Imaging IEEE Trans. Vol. 25. IEEE; 2006. Cluster analysis of dynamic cerebral contrast-enhanced perfusion MRI time-series; p. 62-73.
31. Otto TD, Meyer-Bäse A, Hurdal M, Sumners D, Auer D, Wismüller A. Model-free functional MRI analysis using cluster-based methods. AeroSense. 2003; 2003:17–24.
32. Huber, MB., Lancianese, SL., Nagarajan, MB., Ikpot, IZ., Lerner, AL., Wismüller, A. Biomed Eng IEEE Trans. Vol. 58. IEEE; 2011. Prediction of biomechanical properties of trabecular bone in MR images with geometric features and support vector regression; p. 1820-1826.
33. Meyer-Bäse, A., Pilyugin, SS., Wismüller, A. Stability analysis of a self-organizing neural network with feedforward and feedback dynamics. Neural Networks, 2004. Proceedings. 2004 IEEE Int Jt Conf; 2004. p. 1505-1509.
34. Wismüller, A., Meyer-Bäse, A., Lange, O., Schlossbauer, T., Kallergi, M., Reiser, MF., Leinsinger, G. J Electron Imaging. Vol. 15. International Society for Optics and Photonics; 2006. Segmentation and classification of dynamic breast magnetic resonance image data. 13020-013020-13
35. Nagarajan, MB., Huber, MB., Schlossbauer, T., Leinsinger, G., Krol, A., Wismüller, A. Mach Vis Appl. Vol. 24. Springer; Berlin Heidelberg: 2013. Classification of small lesions in dynamic breast MRI: eliminating the need for precise lesion segmentation through spatio-temporal analysis of contrast enhancement; p. 1371-1381.
36. Nagarajan, MB., Huber, MB., Schlossbauer, T., Leinsinger, G., Krol, A., Wismüller, A. J Med Biol Eng. Vol. 33. NIH Public Access; 2013. Classification of Small Lesions in Breast MRI: Evaluating The Role of Dynamically Extracted Texture Features Through Feature Selection.
37. Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C. A four-dimensional probabilistic atlas of the human brain. Journal of the American Medical Informatics Association. 2001; 8(5):401–430. [PubMed: 11522763]
38. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004; 23:S208–S19. [PubMed: 15501092]
39. Wismüller A, Lange O, Dersch DR, Leinsinger GL, Hahn K, Pütz B, Auer D. Cluster analysis of biomedical image time-series. International Journal of Computer Vision. 2002; 46:103–128.

40. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002; 15(1):273–89. [PubMed: 11771995]
41. Granger CW. Testing for causality: a personal viewpoint. *Journal of Economic Dynamics and control*. 1980; 2:329–352.
42. GMLVQ Toolbox: <http://matlabserver.cs.rug.nl/gmlvqweb/web/>

Figure 1.

Flowchart of the steps involved to classify controls from patients using resting-state fMRI. First, resting-state fMRI data is preprocessed following which regional time-series are extracted. Subsequently, we obtain the IsGC connectivity matrix. Such matrices are obtained for every subject. The vectorized matrices represent every subject as the resting-state connectivity of their brain. Since HIV associated Neurocognitive Disorder (HAND) causes neurodegeneration, we use machine learning to classify the two groups.

Figure 2.

Connectivity matrices for a single subject. (LEFT) lsGC connectivity matrix when $c = 2$. (CENTER) lsGC connectivity matrix when $c = 20$. (RIGHT) cGC connectivity matrix. All the above matrices were constructed with model order $d = 2$.

Figure 3.

Plots comparing lsGC with cGC. (LEFT) plot of mean AUC values over 100 iterations. Stars (*) correspond to those orders at which lsGC with $c=2$ and $c=20$ (orange and yellow) are significantly better than cGC. (RIGHT) plot of mean accuracy values over 100 iterations. Stars (*) correspond to those orders at which lsGC with $c=2$ (orange) is significantly better than cGC. The purple circle (O) corresponds to the order at which cGC was better than lsGC with $c=1$. Significance is considered at $p < 0.01$.