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Autism Spectrum Disorder Diagnosis Using Sparse Graph Embedding of Morphological Brain Networks

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Abstract. Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder involving a complex cognitive impairment that can be difficult to diagnose early enough. Much work has therefore been done investigating the use of machine-learning techniques on functional and structural connectivity networks for ASD diagnosis. However, networks based on the morphology of the brain have yet to be similarly investigated, despite research findings that morphological features, such as cortical thickness, are affected by ASD. In this paper, we first propose modelling morphological brain connectivity (or graph) using a set of cortical attributes, each encoding a unique aspect of cortical morphology. However, it can be difficult to capture for each subject the complex pattern of relationships between morphological brain graphs, where each may be affected simultaneously or independently by ASD. In order to solve this problem, we therefore also propose the use of high-order networks which can better capture these relationships. Further, since ASD and normal control (NC) high-dimensional connectomic data might lie in different manifolds, we aim to find a low-dimensional representation of the data which captures the intrinsic dimensions of the underlying connectomic manifolds, thereby allowing better learning by linear classifiers. Hence, we propose the use of sparse graph embedding (SGE) method, which allows us to distinguish between data points drawn from different manifolds, even when they are too close to one another. SGE learns a similarity matrix of the connectomic data graph, which then is used to embed the high-dimensional connectomic features into a low-dimensional space that preserves the locality of the original data. Our ASD/NC classification results outperformed several state-of-the-art methods including statistical feature selection, and local linear embedding methods.

1 Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by varied impairments in cognitive function, including difficulties with social communication and interaction, language, and restricted, repetitive behaviours. This has made diagnosing the disorder a challenging task [1]. However, aided by

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recent technological and methodological advances in neuroimaging tools, there has been growing interest in understanding how ASD can alter the connectivity between different regions within the brain, and how this information may be leveraged to help diagnose the disorder with greater accuracy [2]. The two most widely used measures of brain connectivity used for investigating ASD in the literature are functional connectivity and structural connectivity, derived from functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) respectively, with literature reviews available for both types of data [3,4]. For example, all 77 studies discussed in [5]'s review of using machine learning on connectomes (networks of the brain) to predict clinical outcomes used functional and/or structural connectivity networks to do so. Despite this growing body of research on such networks, however, there is still a gap in the literature where morphological networks have not been explored to the same degree. This gap needs to be filled, considering there are studies that indicate morphological features of the brain, such as cortical thickness, can be affected in neurological disorders, including ASD [6,7]. As such, the use of networks based on morphological data in neurological disorder diagnosis, using machine learning, could prove fruitful. Further, such networks have not been used to investigate ASD in the literature so far. In this study, we will therefore aim to define several networks based on the morphology or geometry of the cortical surface of ASD and NC subjects, and investigate their use in diagnosing ASD using machine learning techniques.

Different morphological views of the cortical surface (e.g. cortical thickness and mean curvature) may also have different relationships between them, where they could be affected simultaneously or independently in different regions of the brain by ASD. As a result, there could be a very complex pattern of how ASD affects the different morphological views of the brain. The easiest and most commonly employed method for exploring such relationships is simply to concatenate the multiple networks together so that the data from each view is included in the overall set of data for each subject, unaltered [5]. However, recent research on Alzheimer's Disease has found better results when using High Order Networks (HONs) [8]. These are constructed from low-order (e.g. functional connectivity) networks by, for each view or network, extracting the correlations between different pairs of brain regions, then calculating the correlation between these values across all views, for each pair of brain regions. This method therefore better allows us to capture the higher-order relationships between different views of the brain. However, it has yet to be applied to ASD data in machine learning research, and so, with this study, we also aim to contribute to the literature on the use of such HONs when investigating ASD. One potential problem with the use of HONs, however, is that the networks produced are very large and, as a result, computationally expensive. To mitigate this, feature selection or dimensionality reduction is necessary. Noting that ASD morphological changes between brain regions might be very subtle, the manifolds where both ASD and healthy connectomic data lie might be very close and challenging to embed into a low-dimensional space. To address this problem, we further propose a classifi-

cation framework based on a *sparse graph embedding of connectomic data* using the method developed in [9]. Specifically, we use graph embedding of the HONs, which would allow us to (1) explore the high-order relationships without having to deal with overly large networks, (2) learn the features that are most discriminative in classifying and diagnosing ASD, and (3) investigate the effectiveness of SGE as a dimensionality reduction technique on our data, as compared to other state-of-the-art methods.

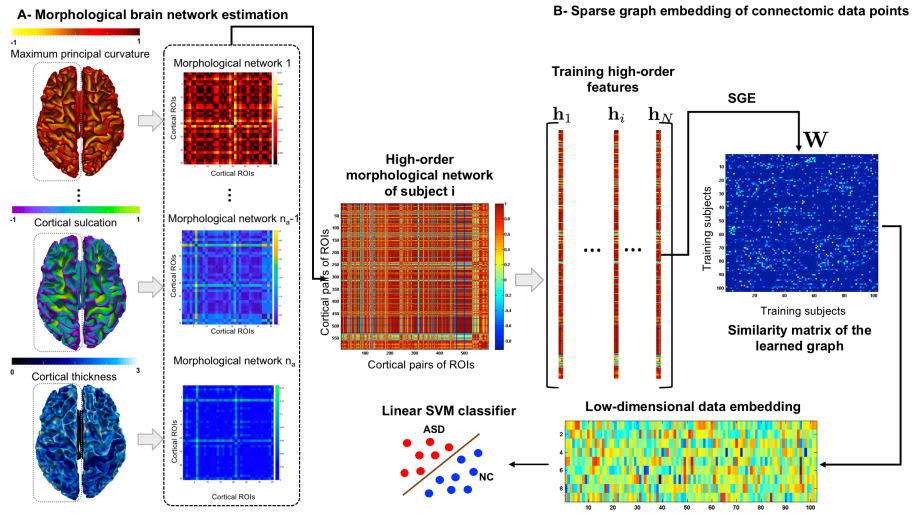

Fig. 1: *High-order sparse graph embedding (SGE) of high-order brain networks for classifying autism spectrum disorder (ASD) and healthy brains.* (A) For each subject i, we construct n_a low-order morphological networks for each cortical attribute. Then, we merge these into a high-order network represented by a feature vector $\mathbf{h}_i$. (B) Given the high-order feature matrix of all subjects, we use sparse graph embedding [9] to learn a sparse similarity matrix $\mathbf{W}$ of a graph $\mathcal{G}$ which models the relationship between data points lying in different connectomic manifolds. Next, we embed the graph into a low-dimensional space where a linear SVM classifier is trained.

2 Proposed Sparse Graph Embedding of High-Order Morphological Brain Networks for Autism classification

In this section, we present our sparse graph embedding (SGE) of high-order morphological brain networks for ASD classification using the SMCE method proposed in [9]. We denote matrices by boldface capital letters, e.g., $\mathbf{X}$, and scalars are denoted by lowercase letters, e.g., x. For easy reference, we have summarized the major mathematical notations in **Table** 1. **Fig.** 1 illustrates the proposed pipeline for ASD/NC classification in four major steps: (1) construction

Table 1: *Major mathematical notations used in this paper.*

Mathematical notation	Definition
$\mathbf{C}_i^a = (V_C, E_C)$	low-order brain network graph $\mathbb{R}^{n_r \times n_r}$ of a single subject i for cortical attribute a
V_C	nodes or brain ROIs of size n_r
E_C	edges connecting pairs of brain ROIs in a single subject
n_a	number of cortical attributes
$\mathbf{H}_i = (V_H, E_H)$	high-order brain network graph of a single subject i
V_H	a node represents a pair of brain ROIs
E_H	edges connecting two pairs of brain ROIs in a single subject
$\mathbf{h}_i$	high-order connectomic feature vector $\in \mathbb{R}^{\mathbb{D}}$ of subject i derived from brain graph $\mathbf{H}_i$
N	number of training subjects
K	number of manifolds
$\mathcal{M}_l$	manifold where similar connectomic data points lie
d_l	intrinsic dimension of manifold $\mathcal{M}_l$
$\mathcal{G} = (V_{\mathcal{M}}, E_{\mathcal{M}})$	similarity graph of connectomic data points nested in different manifolds $\{\mathcal{M}_l\}_{l=1}^K$
$\hat{\mathbf{D}}_i$	normalized distance matrix in $\mathbb{R}^{D \times N-1}$ between current data point $\mathbf{h}_i$ and other data points
$\mathbf{Q}_i$	positive-definite diagonal proximity inducing matrix
α_i	a sparse vector whose $d_l + 1$ nonzero elements correspond to $d_l + 1$ neighbours of $\mathbf{h}_i \in \mathcal{M}_l$
$\mathbf{w}_i$	weight vector in $\mathbb{R}^N$ associated with the i-th point
$\mathbf{W}$	similarity matrix in $\mathbb{R}^{N \times N}$ of graph $\mathcal{G}$

of low-order morphological networks, 2) construction of high-order morphological network, 3) connectomic feature extraction, and 4) sparse graph learning and embedding to reduce the dimension of the extracted features for our target classification task.

Low-order morphological network construction. For each subject i and each cortical attribute a (e.g., cortical thickness), we build a brain graph $\mathbf{C}_i^a = (V_C, E_C)$, where each node in V_C represents a cortical region of interest (ROI), and each edge in E_C connecting two ROIs R_p and R_q is defined as $\mathbf{C}_i(p,q) = |\hat{x}_p - \hat{x}_q|$, where $\hat{x}_p$ denotes the average of the cortical attribute across all vertices in region R_p. Given n_a cortical attributes, we generate for each cortical hemisphere n_a morphological brain graphs $\{\mathbf{C}_a\}_{a=1}^{n_a}$.

High-order morphological network construction (HON). We note that ASD might affect not only region-to-region morphological brain connections on a low-order level, but also high-order relationships between pairs of ROIs, where complex interactions between sets of ROIs might be affected. Hence, we propose constructing a high-order morphological network to integrate into a single, larger brain graph $\mathbf{H}_i = (V_H, E_H)$ all low-order brain graphs $\{\mathbf{C}_a\}_{a=1}^{n_a}$ of *both* hemispheres. Each node in V_H denotes a *pair* of ROIs and each edge in E_H connecting two pairs or ROIs (p,q) and (p',q') denotes the Pearson Correlation coefficient between vectors $\mathbf{y_{pq}}$ and $\mathbf{y_{p'q'}}$, where $\mathbf{y_{pq}}$ corresponds to the connectivity strength between the p-th and q-th ROIs across all $2n_a$ brain networks in both hemispheres.

Feature Extraction. We propose two types of features: high-order features (HON), and concatenated low-order features (CON). Noting that all brain graphs are symmetric, for each subject i, we represent its high-order brain graph as a matrix $\mathbf{H}_i$, then concatenate its upper triangle elements into a long feature vector $\mathbf{h}_i$. The weights on the diagonal are set to zero to avoid self-connectedness. For low-order brain graphs $\{\mathbf{C}_a\}_{a=1}^{n_a}$, we simply concatenate the upper triangle elements across all cortical attributes into a feature vector (termed as CON). To address the issue of 'high-dimensional features vs.a low sample size' in classifi-

cation, we propose embedding our high-dimensional connectomic features into a low-dimensional space where we can efficiently train a linear classifier through learning a sparse graph.

Sparse graph embedding (SGE) using connectomic brain features for ASD classification. Since ASD and NC high-dimensional connectomic data might lie in different manifolds, we aim to find a low-dimensional representation of the data which captures the intrinsic dimensions of the underlying connectomic manifolds, thereby allowing better learning by classifiers. However, since morphological brain changes can be very subtle in autistic subjects compared with healthy brains, their data manifolds can be very close to each other. Hence, estimating a low-dimensional embedding that allows us to distinguish between data points drawn from different manifolds is challenging. To solve this problem, Elhamifar *et al.* proposed a robust algorithm for sparse manifold clustering and embedding (SMCE) that efficiently handles multiple manifolds that are very close to each other [9]. This is achieved through encouraging a sparse selection of nearby connectomic points that lie in the same manifold and spanning a low-dimensional affine subspace. Unlike typical dimensionality reduction methods such as local linear embedding (LLE), which builds a neighbourhood graph by connecting each data point to a *fixed* number of nearest points, SMCE learns a graph neighbourhood automatically, thereby allowing the neighbourhood size on the manifold to vary. This better handles variation in the density of data points on the manifold.

Leveraging the strengths of the SMCE method, we then propose our sparse graph embedding (SGE) framework for the low-dimensional representation of the high-order connectomic brain manifolds of ASD and NC subjects (**Fig.** 1). Given N training high-order feature vectors $\{\mathbf{h}_i \in \mathbb{R}^D\}_{i=1}^N$ lying in K different manifolds $\{\mathcal{M}_{l=1}^K\}$ of intrinsic dimensions $\{d_l\}_{l=1}^K$, we build a similarity graph $\mathcal{G} = (V_\mathcal{M}, E_\mathcal{M})$, where each node in $V_\mathcal{M}$ represents a feature vector $\mathbf{h}$ derived from a brain graph $\mathbf{H}$. Our goal is to learn sparse connections in graph $\mathcal{G}$ through connecting each point to a few neighbouring points with appropriate weights such that the selected neighbouring points are from the same manifold. This is achieved through solving a sparse optimization function that selects for each connectomic point $\mathbf{h}_i \in \mathcal{M}_l$ *a few* neighbouring points that span a low-dimensional affine subspace passing near $\mathbf{h}_i$:

$$\min_{\alpha_i} \lambda||\mathbf{Q}_i\alpha_i||_1 + \frac{1}{2}||\check{\mathbf{D}}_i\alpha_i||_2^2 \; s.t. \; \mathbf{1}^T\alpha_i = 1, \tag{1}$$

where $\alpha_i^T \triangleq [\alpha_{i1} \dots \alpha_{iN}]$ denotes a solution whose d_l+1 nonzero elements correspond to $d_l + 1$ neighbours of $\mathbf{h}_i \in \mathcal{M}_l$. $\check{\mathbf{D}}_i$ represents the normalized distance matrix between current data point $\mathbf{h}_i$ and other points: $\check{\mathbf{D}}_i \triangleq [\frac{\mathbf{h}_1-\mathbf{h}_i}{||\mathbf{h}_1-\mathbf{h}_i||_2} \dots \frac{\mathbf{h}_N-\mathbf{h}_i}{||\mathbf{h}_N-\mathbf{h}_i||_2}] \in \mathbb{R}^{D\times N-1}$. L_1 sparsity penalty constrains points closer to $\mathbf{h}_i$ to be less penalised than points that are further away. $\mathbf{Q}_i$ is a proximity inducing positive-definite diagonal matrix, which favours the selection of close points to the current point $\mathbf{h}_i$ through assigning smaller weights to them. We define its diagonal elements as

Table 1. *ASD/NC classification results using our method and different comparison methods.*

Features	Accuracy (%)	Sensitivity (%)	Specificity (%)
View 1 (Raw)	51.9608	48.8372	54.2373
View 2 (Raw)	53.9216	44.1860	61.0169
View 3 (Raw)	47.0588	37.2093	54.2373
View 4 (Raw)	47.0588	41.8605	50.8475
CON (Raw)	52.9412	37.2093	64.4068
HON (Raw)	52.9412	44.1860	59.3220
CC(HON) (Raw)	46.0784	32.5581	55.9322
HON + CON (Raw)	53.9216	46.5116	59.3220
CC(HON) + CON (Raw)	51.9608	39.5349	61.0169
CC(HON) (T-Test)	47.0588	32.5581	57.6271
HON + CON (T-test)	55.8824	37.2093	69.4915
CC(HON) + CON (T-test)	52.9412	37.2093	64.4068
CC(HON) (LLE)	58.8235	60.4651	57.6271
HON + CON (LLE)	50.9804	55.8140	47.4576
CC(HON) + CON (LLE)	43.1373	32.5581	50.8475
CC(HON) (SGE)	52.9412	62.7907	45.7627
HON + CON (SGE)	50	51.1628	49.1525
CC(HON) + CON (SGE)	**61.7647**	**62.7907**	**61.0169**

$\frac{||\mathbf{h}_j - \mathbf{h}_i||_2}{\sum_{t \neq i} ||\mathbf{h}_t - \mathbf{h}_i||_2} \in (0, 1]$). The trade-off parameter λ balances the sparsity solution (first term) and the affine reconstruction error (second term).

After solving **Eq.** 1, we define a weight vector $\mathbf{w}_i^T = [w_{i1} \dots w_{iN}] \in \mathbb{R}^N$ associated with the i-th point as: $w_{ii} = 0$ and $w_{ij} \triangleq \frac{\alpha_{ij}/||\mathbf{h}_j - \mathbf{h}_i||_2}{\sum_{t \neq i} \alpha_{it}/||\mathbf{h}_t - \mathbf{h}_i||_2}$, $j \neq i$. Ideally, non-zero elements of $\mathbf{w}_i$ will correspond to sparse neighbours of $\mathbf{h}_i$ which belong to the same manifold. Next, we use these weights to define edges in the similarity graph $\mathcal{G}$ where a node $\mathbf{h}_i$ connects to node $\mathbf{h}_j$ with weight $|w_i j|$. Ideally, points in the same manifold will belong to the same connected component in the learned graph $\mathcal{G}$. Ultimately, we define the similarity matrix $\mathbf{W} \triangleq [|\mathbf{w}_1| \dots |\mathbf{w}_N|]$ in $\mathbb{R}^{N \times N}$ of the manifold graph $\mathcal{G}$, which groups points from the same manifold into a block-by-block matrix structure. We then generate the local embedding of the connectomic features by taking the last eigenvectors of the normalized Laplacian matrix associated with each cluster in $\mathbf{W}$. In the training stage, we learn $\mathbf{W}_{tr}$ for all training subjects. Then we use the produced low-dimensional features to train a linear support vector machine (SVM) classifier. In the testing stage, we map the testing subject to a low-dimensional space (with same dimension) through estimating a new $\mathbf{W}_{ts}$ that includes training and testing samples.

3 Results and Discussion

Evaluation dataset and method parameters. We used leave-one-out cross validation to evaluate the proposed classification framework on 102 subjects (59 ASD and 43 NC) from Autism Brain Imaging Data Exchange (ABIDE I)[1] public dataset, each with structural T1-w MR image [10]. We used FREESURFER to reconstruct both right and left cortical hemispheres for each subject from T1-w MRI. Then we parcellated each cortical hemisphere into 35 cortical regions using Desikan-Killiany Atlas. For each subject, we generated $n_a = 4$ cortical morphological networks: $\mathbf{C}^1$ denotes the maximum principal curvature brain view, $\mathbf{C}^2$ denotes the mean cortical thickness brain view, $\mathbf{C}^3$ denotes the mean sulcal depth brain view, and $\mathbf{C}^4$ denotes the mean of average curvature. For SGE parameters, we set $\lambda = 10$. For both LLE and SGE, we used nested grid-search to estimate the low dimension of the feature embedding (9 for SGE and 50 for LLE).

Method evaluation and comparison methods. We compared our method with three state-of-the-art methods: (RAW) where we directly input the raw connectomic brain features, (t-test) where we perform dimensionality reduction using statistical feature selection, and (LLE) where we perform a local linear embedding of the connectomic features to produce a compact and low-dimensional representation of feature vectors. Since both CON and HON feature vectors are high-dimensional, we propose a preliminary dimensionality reduction step through representing each network by a clustering coefficients (CC) feature vector. This will allow us to benchmark our method against the recent connectomic classification framework proposed in [8] where they first concatenated the clustering coefficients of the functional HON (CC(HON)) and CON features (i.e., CC(HON) + CON), then performed t-test for feature selection to train an SVM classifier for Alzheimer's disease diagnosis. We further evaluated all methods using combinations of different feature types: (1) HON, (2) CON, (3) CC(HON), (4) HON + CON, and (5) CC(HON) + CON. All results are presented in **Table** 1 and **Fig.** 2. Our method produced the best ASD/NC classification accuracy (61.76%) when using (CC(HON) + CON) features, which largely outperformed t-test using (CC(HON) + CON) as in [8].

4 Conclusion

We proposed a sparse graph learning framework for classifying disordered brain connectivities based on the morphology of cortical hemispheres. Specifically, we estimated a local embedding of high-order and low-order morphological brain networks for distinguishing between autistic and healthy brains. Given that morphological brain changes are subtle in ASD patients, our results are promising. Instead of performing the local embedding of data points for each feature type independently, we will further extend our method to jointly embed different

[1] http://fcon_1000.projects.nitrc.org/indi/abide/

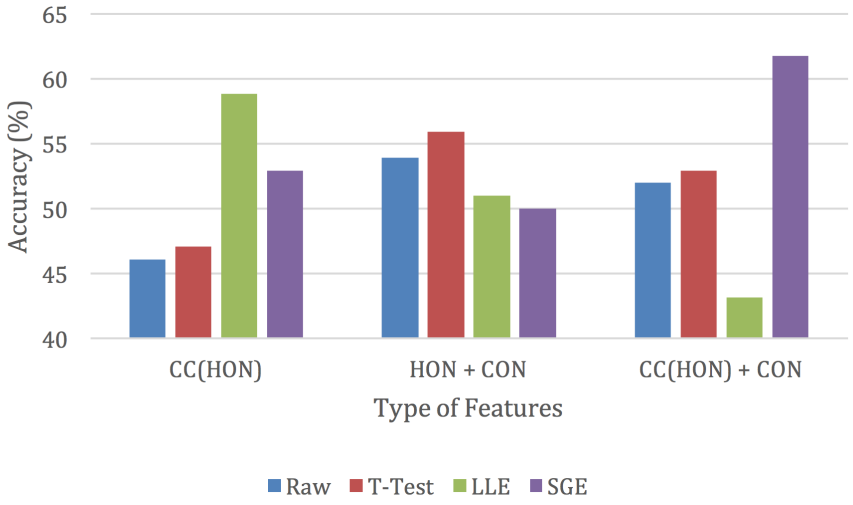

Fig. 2: *ASD/NC classification accuracies for our method (SGE) and other comparison methods using combinations of different connectomic feature types.* We compared our method with three state-of-the-art methods: (RAW) where we directly input the raw connectomic brain features, (t-test) where we perform dimensionality reduction using statistical feature selection, and (LLE) where we perform a local linear embedding of the connectomic features to produce a compact and low-dimensional representation of feature vectors. Our method produced the best ASD/NC classification accuracy when using (CC(HON) + CON) features, which significantly outperformed t-test using (CC(HON) + CON) as in [8].

feature types nested in multiple views of the same manifold (e.g., ASD data manifold).

References

1. Lord, C., Cook, E.H., Leventhal, B.L., Amaral, D.G.: Autism spectrum disorders. Neuron **28** (2000) 355 – 363 1
2. Anagnostou, E., Taylor, M.J.: Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. Molecular Autism **2** (2011) 4 2
3. Philip, R.C., Dauvermann, M.R., Whalley, H.C., Baynham, K., Lawrie, S.M., Stanfield, A.C.: A systematic review and meta-analysis of the fmri investigation of autism spectrum disorders. Neuroscience Biobehavioral Reviews **36** (2012) 901 – 942 2
4. Stanfield, A.C., McIntosh, A.M., Spencer, M.D., Philip, R., Gaur, S., Lawrie, S.M.: Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies. European Psychiatry **23** (2008) 289 – 299 Neuroimaging. 2

5. Brown, C., Hamarneh, G.: Machine learning on human connectome data from MRI. arXiv:1611.08699v1 (2016) 2
6. Cauda, F., Costa, T., Nani, A., Fava, L., Palermo, S., Bianco, F., Duca, S., Tatu, K., Keller, R.: Are schizophrenia, autistic, and obsessive spectrum disorders dissociable on the basis of neuroimaging morphological findings?: A voxel-based meta-analysis. Autism Research (2017) 2
7. Khundrakpam, B.S., Lewis, J.D., Kostopoulos, P., Carbonell, F., Evans, A.C.: Cortical thickness abnormalities in autism spectrum disorders through late childhood, adolescence, and adulthood: A large-scale mri study. Cerebral Cortex **27** (2017) 1721 2
8. Chen, X., Zhang, H., Gao, Y., Wee, C.Y., Li, G., Shen, D., the Alzheimer's Disease Neuroimaging Initiative: High-order resting-state functional connectivity network for mci classification. Human Brain Mapping **37** (2016) 3282–3296 2, 7, 8
9. Elhamifar, E., Vidal, R.: Sparse manifold clustering and embedding. (2011) 55–63 3, 5
10. Mueller, S.G., Weiner, M.W., Thal, L.J., Petersen, R.C., Jack, C., Jagust, W., Trojanowski, J.Q., Toga, A.W., Beckett, L.: The Alzheimer's Disease Neuroimaging Initiative. Neuroimaging Clinics of North America **10** (2005) 869–877 7