MRI Based Machine Learning for Identification of Novel Subtypes in Autism

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In this study of children with idiopathic autism, multivariate unsupervised and supervised learning of structural magnetic resonance images (MRI) revealed a novel subtype of autism that was characterized by meaningful grey matter anomalies and was predictive of behavioral outcome. Given that previous studies have failed to identify neurobiological subtypes of autism that are clinically meaningful, these findings underscore (a) the importance of utilizing machine learning algorithms to explore neurobiological motifs, and (b) the potential utility of brain-based machine learning in clinical practice.

I. Introduction

AUTISM is currently the fastest growing developmental disability [1]. However, despite the increasing prevalence of autism, little is known about its causes or cures and exploration into developmental prognosis has been stunted by the low predictive validity of behavioral measures [2]. Leshner et al, argue that this contemporary lack of understanding stems from the inability to identify biologically significant sub populations [3]. Using Leshner's analysis as inspiration the goal of this paper is to apply machine learning towards unraveling new neurological based subtypes.

In this analysis we cluster segmented grey matter from MRI scans of 113 boys (μ age = 2.77 years, $\sigma^2 = 0.63$); 63 diagnosed with Autism, 31 typically developing (TD) controls and 19 controls with idiopathic developmental delay (DD), and examine if these clusters are clinically meaningful. Our approach to this problem forms a natural application for machine learning and can be viewed as an instance of unsupervised learning on high-dimensional, noisy data. The measure of success that we use is: clusters that define a subtype of Autism must (1) be robust and quantitatively distinct, (2) have significant correlation with measurable behaviors and (3) reflect plausible neurobiological patterns which are associated with the observed behaviors.

Previous biologically based analysis of autism has attempted to categorize the disorder through univariate or coarse multivariate brain regions and until now has been unable to determine explicit subtypes. The seminal paper in this area by Hrdlicka et al amalgamated the fine grey matter MRI information into seven coarse brain measurements based on strong *a priori* assumptions [4]. Though their results were instrumental in demonstrating the potential for analyzing structural MRI, they were unable to deduce meaningful patterns. Implementing their methodology on our data set demonstrates subtypes that are not distinct by general measures and hold no behavioral correlations. Given autism has an intricate neural foundation, we hypothesize that; a coarse feature reduction could hide information critical for understanding patterns in autistic brains. Based on this hypothesis we perform a novel application of unsupervised learning methodology directly onto carefully preprocessed high dimensional fine grey matter volume autistic MRI scans.

This unique application produces results that significantly improve on the industry standard of behavioral prognosis and reveals clusters that meet the initial subtype criteria.

II. Pre-processing

We are provided grey matter data derived from MRI Scans that were mapped into a standard 4mm voxel brain space using modulated Spatial Normalization. Additional preprocessing is performed as follows:

Initially, we adjust our data for age, scan site and total grey matter volume. Values are adjusted by performing linear multiple regression with age, scan site and total GM volume as independent variables and subtracting the calculated residuals from the MRI data.

Then, due to the sparse high dimensional nature of our data we choose to reduce the number of voxels considered. We try to eliminate voxels based on (a) recursive feature elimination using weights from a linear Support Vector Machine (SVM) that separates autistic subjects from controls, (b) regression between each voxel and temporal change in behavior characteristics and (c) an upper bound selection of brains areas found to be important for autism based on research by Amaral et al [5]. Of the feature reduction methods considered, the Amaral based reduction produces the best performance improvement.

Overall these preprocessing steps result in a higher degree of uniformity across all subjects and reduce the level of noise in the data. This preprocessing yields 163% improvement in cluster strength (measured as CCC, refer to section III).

III. Unsupervised clustering

One of the most crucial steps in this analysis is to identify robust, quantitatively distinct clusters within the set of autistic patients. To obtain these clusters we apply three separate unsupervised techniques commonly used in the field of structural MRI analysis: Hierarchical Agglomerative Clustering (HAC), Spectral Clustering (SC) and General Mixture Models (GMM).

1. HAC Clustering

Recently, Stedman et al demonstrated the use of HAC on grey matter MRI data in order to uncover nuanced neural patterns [6]. Given this precedent, we apply HAC to our dataset. To agglomerate clusters, we use a Ward linkage criterion that minimizes the error of sum squares with the Euclidean Squared Distance dissimilarity metric. In contemporary structural MRI and brain psychology literature, Euclidean distance has been demonstrated to be an accurate dissimilarity metric [7] and Ward linkage is an efficient way to obtain clusters with minimized variance.

This method provides two distinct clusters: a larger cluster of 46 autistic children, which we refer to as the Alpha Cluster, and a smaller cluster of 17 autistic children, which we refer to as the Beta Cluster. To objectively determine the correctness of HAC we apply the HAC specific Cophenetic Correlation Coefficient (CCC) test scaled from 0 to 1 where 1 represents the ideal CCC and 0.5 is the threshold for considering a cluster to be significant [8]. The clusters obtain a CCC value of 0.8144, which is strong evidence that HAC has identified two natural clusters.

To visually demonstrate these results we project clusters Alpha and Beta onto the primary principle components (PC) (see *Figure 1*). While only 14% of the entire brain matrix can be represented on three PCs, the first three PCs reflect 93% of the variance between the clusters.

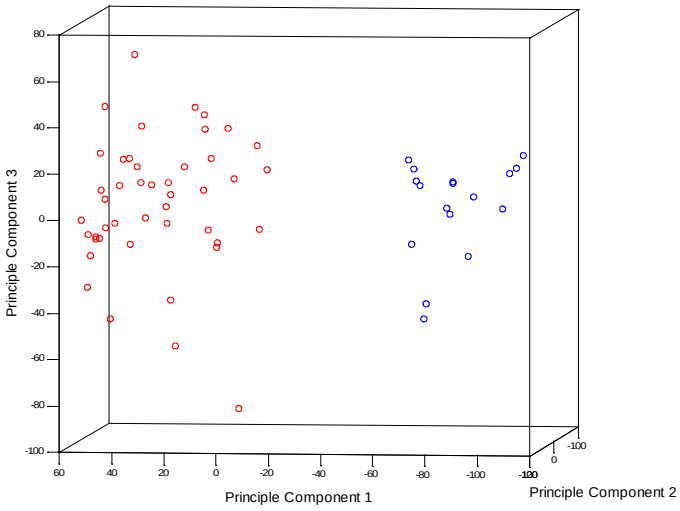

Figure 1: Alpha (red) and Beta (blue) Clusters

2. Spectral Clustering

As demonstrated by Wassermann et al [9], SC is well-suited choice for sparse data such as MRI scans. The SC algorithm uses the spectrum of the data point similarity matrix to retain select features that cause maximum intra-cluster similarity and minimum inter-cluster similarity. Though this method produces slightly different cluster labels, the results are 95% similar to those obtained using HAC.

3. General Mixture Models

Another clustering method commonly used in the domain of MRI scans is GMM. This method uncovers two independent component distributions with high peaks, which implies there are two tight clusters. The labels obtained through GMM are identical to those obtained from SC and are highly similar to those found using HAC.

These three independent clustering methods obtain highly similar clusters. This supports the hypothesis that the dataset of autistic children has two natural clusters and that the Alpha and Beta clusters are legitimate.

General Clustering Validation

Even though the clusters appear to be highly distinct, to consider them to be formal subtypes we must show that: (1) these clusters are numerically separate when measured using general cluster tests and (2) they give the same results when the input is perturbed by an appropriate amount of noise. To test these criteria we use Homogeneity-Separation (HS), Silhouette, and Weighted Average Discrepant Pairs (WADP) general cluster validation measures. HS measures the ratio of homogeneity to separation where separation is the average Euclidean distance between clusters weighted by cluster size. Silhouette measures the ratio of homogeneity to separation where separation for sample i is the max Euclidean distance from i to another sample j normalized to the range -1 to 1. WADP measures how many cluster labels change when each matrix feature is perturbed by normally distributed noise with mean 0 and variance equal to the log-ratio of that feature across all samples [10]. We repeat each of the tests for different number of clusters (k) to confirm that the analysis should be performed on two clusters. HS and Silhouette are maximized and WADP discrepancy is minimized at $k = 2$.

Clustering	HS Ratio	Silhouette	WADP
HAC	2.14	0.429	0.087
GMM / Spec	1.40	0.316	0.293

Figure 2: General Validation Measures

We observe that HAC clustering outperforms both GMM and SC. Thus we continue subtype analysis using the Alpha and Beta clusters. Moreover, HAC performed well on all three validation tests. The high HS Ratio and Silhouette scores quantitatively demonstrate that the variance between the Alpha and Beta clusters is more significant than the variance within each cluster. The WADP test shows that the clusters give the same results even with additional noise.

Finally, to confirm the validity of the entire process we

apply the same pre-process and clustering methodology to a combined set of control and autistic MRI scans. This approach yields three clusters (CCC of 0.8125); a Control Cluster, the Alpha Cluster and the Beta Cluster. Since the preprocessing steps used in this paper and the Euclidean HAC clustering algorithm successfully separate the control brains from autistic brains we conclude that our procedure is applicable to the domain of autistic MRI scans.

IV. Behavior Characterization of Clusters

Our next step is to determine whether there are meaningful trends between the Alpha and Beta clusters and the behaviors of the corresponding autistic children. For each child, behavioral data was measured using a set of quantifiable tests, which are typically used to diagnose or characterize autism. These tests were performed once at the time when the structural MRI scans were taken (Time Initial tests denoted T_0) and again after two to three years. Our longitudinal tests are performed on the variability measured as change in score per year (Slope tests denoted Δ) to account for inconsistency in how much time elapsed between the two tests for each patient. In order to explore possible trends, we apply univariate, linear multivariate and kernalized multivariate analysis between the Alpha-Beta group labels and the T_0 and Δ tests.

Univariate Analysis

First we run Welsh's Null Hypothesis univariate tests (WNH), a version of the standard T-Test that accounts for different sample sizes, on the behavior characteristics of the Alpha and Beta subgroups. For each set of scores for a behavior, b such that $b \in \Delta \cup T_0$ we split the scores by their Alpha and Beta labels. We then run NHT to test the hypothesis that the two sets of scores are samples from the same Gaussian distribution against the hypothesis that they are samples from separate Gaussians. The general threshold for discarding the null hypothesis is a p value of 0.05.

Of the behavioral tests, the ADI Repetitive and Stereotyped Behavior (ADI_RS) test and the ADOS Stereotyped (ADOS_S) test, two distinct measures of a child's repetitive physical behavior of Autism, such as hand flapping and body rocking (referred to by Amaral et al as Repetitive Behaviors), pass the NHT with significance measures of p = 0.0030 and p = 0.034 respectively. However to take into account the probability of false positives given multiple tests, we apply the Bonferroni Correction [11], resulting in a stringent p threshold of 0.0033. Since the significance level of ADI_RS test is below the Bonferroni threshold, it is exceedingly likely that the ADI_RS distinction (*Figure 3*) is a strong Alpha Beta correlation. Another interesting observation is that in both the ADI_RS and ADOS_S slope behavior tests, the autistic children in the Beta cluster had positive mean values (ADI_RS μ = 0.51) while the autistic children in the Alpha cluster had negative mean values (ADI_RS μ = -0.89). This suggests that the Repetitive symptoms of Alpha group improved over time whereas the repetitive symptoms of the Beta group worsened.

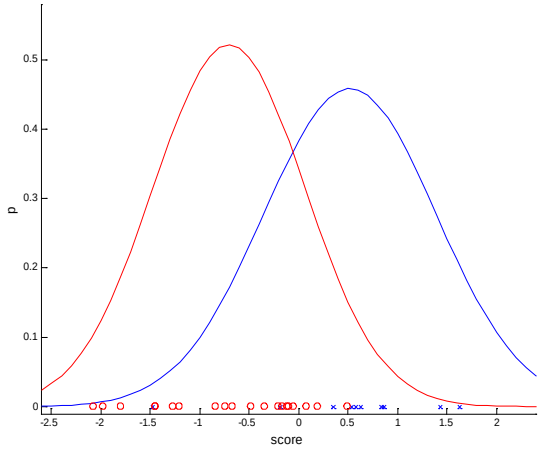

Figure 3: ADI_RS test showing the Alpha distribution (red) and Beta distribution (blue)

This is a highly noteworthy result as it shows that the two natural clusters uncovered have a strong univariate longitudinal behavioral trend.

Multivariate Analysis

In order to determine how well our labels could predict a collection of behaviors, we perform multivariate analysis between the discovered groups and the recorded behavior scores. This experiment was implemented using a SVM classifier with a linear kernel between the Alpha Beta cluster labels and both the T_0 and Δ behaviors. To measure how well the SVM could separate behavior trends with respect to each cluster, we use leave-one-out cross validation (LOOCV) to calculate accuracy (ACC), sensitivity (SEN), specificity (SPE), positive predictive value (PPV) and negative predictive value (NPV).

To understand how our results compare to chance we apply a Permutation Analysis (PA) algorithm that calculates the mean (μ) and standard deviation (σ) of each metric (under the assumption that the metrics are distributed normally) and use the resulting distribution to homogenize our results. In order to evaluate μ_i and σ_i such that $i \in metrics$ we repeat the following process until μ_i and σ_i converge: (1) assign random cluster labels in proportion to each subject, (2) evaluate how an SVM performs, measured by metric I (3) update μ_i and σ_i to incorporate the results.

Metric	Slope	Time Initial
ACC	92.5	83.5
SEN	64.3	74.4
SPE	96.6	84.1
PPV	83.4	80.2
NPV	80.8	77.8

Figure 4: Behavior SVM Metric Percentiles

Using the SVM with clusters Alpha and Beta we obtain the above LOOCV results (*Figure 4*).

Since all the LOOCV metrics are substantially above chance (50^{th} percentile) these results imply that there is a robust behavioral distinction (both in T_0 and Δ) between the Alpha and Beta subgroups and demonstrates that the two clusters have behavioral manifestations. Moreover, though the Alpha and Beta clusters perform well at separating T_0, the clusters are substantially better at distinguishing Δ measures; meaning that the Alpha Beta distinction is more precise at predicting future behavior.

Because the behavior matrices are normalized, the weights used by the SVM represent how important each of the behavior tests are in separating the Alpha and Beta clusters.

Behavior Test	Slope Weights
ADI Repetitive and Stereotyped	1.315
ADOS Stereotyped	0.806

Behavior Test	Time Initial
ADI Repetitive and Stereotyped	1.313
Vineland Communication	-0.963

Figure 5: Behavior SVM Weights for Slope and Time Initial

The behavior-test weights in *Figure* 5 are important for three reasons (1) The most substantial differences in the weights, especially for Δ, are from tests which measured Repetitive and Stereotyped behaviors (2) The parities for the Repetitive behavior tests are internally consistent in denoting that autistic children in the Beta group have more severe symptoms and (3) as expected, the weighted features agree with the univariate analysis. Overall, this demonstrates a meaningful pattern in behaviors and as a result provides powerful evidence for the hypothesis that the Alpha and Beta clusters represent different subgroups of Autism.

Kernalized Multivariate Analysis

To account for potential non-linear relationships between behavior and the Alpha and Beta clusters, we perform multivariate analysis using different kernels. As *Figure 6* demonstrates, the linear kernel out-performs other kernels.

Since the non-linear kernels have high LOOCV testing error with relatively low training error, it seems that the non-linear kernels over-fit the data. This conclusion is reasonable, considering the small training set size relative to number of features used to train the SVM.

Metric	Linear	Quadratic	Radial Basis	Polynomial
ACC	92.5	48.8	61.8	62.3
SEN	64.3	36.7	39.7	93.9
SPE	96.6	57.0	68.0	41.1
PPV	83.4	38.7	50.0	72.8
NPV	80.8	43.1	51.4	78.6

Figure 6: Kernalized SVM Metrics

V. Brain Analysis

The final step in our subtype analysis is to examine the structural MRI differences between the Alpha and Beta clusters. In order to quantify the grey matter differences we use three different methods: (1) We calculate the centroids of the two clusters and find the difference vector between them, (2) We use the primal Eigen-brain, since 92% of the variance between the two clusters is expressed by the first principle component, and (3) We train a SVM to label brains as either Alpha or Beta and extract the weights used by this SVM. For each of the vectors obtained we reconstruct average grey matter brain images by reversing the normalization stages of our preprocessing pipeline.

The brains representative of the difference between the Alpha and Beta clusters (figure 7) show several important patterns. The most prominent and consistent difference that emerges from these brains is the grey matter difference in the Thalamus region (the lower lobes of the Diencephalon, in the center of the brain). Across all three methods of viewing the differences between clusters, the Beta cluster has significantly less grey matter in the core of the Thalamus. Furthermore, in both the centroid and PC brains the Alpha and Beta clusters are distinguished by amount of grey matter in the Orbitofrontal Cortex (The large red activation above the nose) and the Medial Prefrontal Cortex (The thin red strip in front of the Thalamus). Moreover, the Alpha and Beta clusters also show substantial grey matter volume differences in the posterior Vermis of the Cerebellum (the lower region of the Cerebellum) and in the Caudate region.

According to Amaral, two of the four most important regions of the brain for determining Repetitive and Stereotypical Behavior characteristics of autism are the thalamus and the frontal cortex [5]. Moreover, other research has hypothesized that Repetitive Behaviors can also be attributed to the Vermis and the Caudate [12].

Finally the Alpha and Beta clusters also demonstrate differences in the hippocampus (small blue region behind

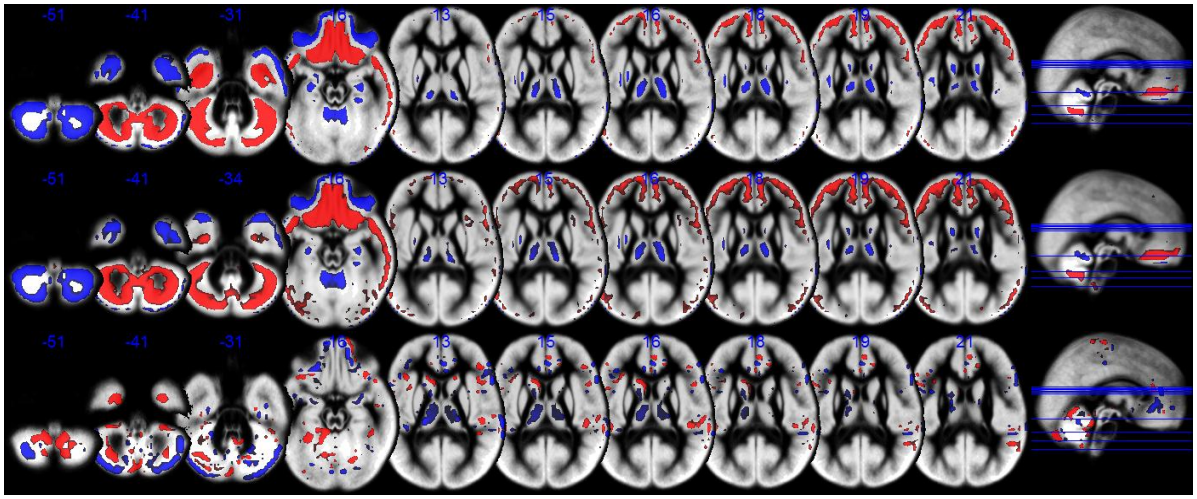

Figure 7: Grey Matter differences measured by centroid difference (top), PCA (middle) and SVM weights (bottom)

the Orbitofrontal cortex). Though this region has not been noted as deterministic for Repetitive behaviors it is considered to be highly significant for Autism in general.

Thus, the regions of the brain with the largest observed differences between the Alpha and Beta group correspond to regions that are thought to cause the behaviors these clusters predicted. This provides strong reinforcement towards the hypothesis that the Alpha and Beta clusters represent meaningful subtypes of Autism. Furthermore, while different regions have been hypothesized individually to cause repetitive behaviors the differences between the Alpha and Beta clusters could lead to further insight on how their combinations affect Repetitive Behaviors in autistic children.

VI. Conclusion

In the hopes of facilitating future diagnosis our project culminated in the development of an autism sub-type classification tool. The classification tool uses SVM to identify whether a patient suffers from Beta autism or not and can make inferences regarding future undesirable behavioral characteristics that the child may suffer from, based on this classification.

Overall this project provides strong evidence that the Beta cluster is a valid subtype of autism that is characterized by repetitive behaviors. Given the possible applications of discovering a new autism subtype, this finding suggests that more exploration should be done to cement understanding of Beta Cluster autism.

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Bibliography

[1] James Rimmer, David Braddock, Kenneth Pitetti – *"Research On Physical Activity And Disability: An Emerging National Priority"* (1996).

[2] Tony Charman, Emma Taylor, Auriol Drew, Helen Cockerill, Jo-Anne Brown, and Gillian Baird – *"Outcome of Children Diagnosed with Autism at Age 2: Predictive Validity"* (2005)

[3] Altevogt BM, Hanson SL, Leshner AI – *"Autism and the environment: challenges and opportunities for research"* (2008).

[4] Hrdlicka M, Dudova I, Beranova I, Lisy J, Belsan T, Neuwirth J, Komarek V, Faladova L, Havlovicova M, Sedlacek Z, Blatny M, Urbanek T - *"Subtypes of autism by cluster analysis based on structural MRI data"* (2005).

[5] Amaral DG, Schumann CM, Nordahl CW - "Neuroanatomy of Autism" (2008).

[6] J.D. Stedman and N.M. Spyrou – *"Hierarchical clustering into groups of human brain regions according to elemental composition"* (1998).

[7] Laurent Itti, Linda Chang, and Thomas Ernst – *"Automatic Scan Prescription for Brain MRI"* (2001).

[8] Sokal, R. R. and Rohlf F. J. – *"The comparison of dendrograms by objective methods"* (1962).

[9] Demian Wassermann, Maxime Descoteaux and Rachid Deriche – *"Recovering cerebral white matter structures with Spectral Clustering of Diffusion MRI Data"* (2007).

[10] Amy V. Kapp and Robert Tibshirani - *"Are clusters found in one dataset present in another dataset?"* (2006).

[11] Hervé Abdi – *"The Bonferonni and Šidák Corrections for Multiple Comparisons"* (2007).

[12] L. Sears, C. Vest, S. Mohamed, J. Bailey and B. Ranson - *"An MRI study of the basal ganglia in autism"* (1999).