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Computer Aided Autism Diagnosis Using Diffusion Tensor Imaging

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ABSTRACT Autism Spectrum Disorder (ASD), commonly known as autism, is a lifelong developmental disorder associated with a broad range of symptoms including difficulties in social interaction, communication skills, and restricted and repetitive behaviors. In autism spectrum disorder, numerous studies suggest abnormal development of neural networks that manifest itself as abnormalities of brain shape, functionality, and/ or connectivity. The aim of this work is to present our automated computer aided diagnostic (CAD) system for accurate identification of autism spectrum disorder based on the connectivity of the white matter (WM) tracts. To achieve this goal, two levels of analysis are provided for local and global scores using diffusion tensor imaging (DTI) data. A local analysis using the Johns Hopkins WM atlas is exploited for DTI atlas-based segmentation. Furthermore, WM integrity is examined by extracting the most notable features representing WM connectivity from DTI. Interactions of WM features between different areas in the brain, demonstrating correlations between WM areas were used, and feature selection among those associations were made. Finally, a leave-one-subject-out classifier is employed to yield a final per-subject decision. The proposed system was tested on a large dataset of 263 subjects from the National Database of Autism Research (NDAR) with their Autism Diagnostic Observation Schedule (ADOS) scores and diagnosis (139 typically developed: 66 males, and 73 females, and 124 autistics: 66 males, and 58 females), with ages ranging from 96 to 215 months, achieving an overall accuracy of 73%. In addition to this achieved global accuracy, diagnostically-important brain areas were identified, allowing for a better understanding of ASD-related brain abnormalities, which is considered as an essential step towards developing early personalized treatment plans for children with autism spectrum disorder.

INDEX TERMS Autism spectrum disorder, connectivity, diffusion, DTI, dwMRI, gray matter and white matter.

I. INTRODUCTION

Autism spectrum disorder is a neuro-developmental syndrome that affects both communications skills, and behavioral and social interaction [1]–[3]. Causes behind ASD are not fully understood, and numerous hypotheses and theories have been proposed for its aetiology. Research suggests that this is a complex or multifactorial condition, wherein both genes and environmental influences offer additive effects for symptom expression. Some investigators hypothesize that ASD symptoms are linked to structural [4] or connectivity [5] anomalies, whereas others suggest a malleable abnormality that ties varying brain functionality to the performance of different tasks [6]. In order to study different types of

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abnormalities correlated with ASD, several magnetic resonance imaging (MRI) based modalities have been used, such as: (i) structural MRI (sMRI) for studying anatomical features, (ii) functional MRI (fMRI) for studying brain activities, and (iii) diffusion tensor imaging (DTI) for studying brain connectivity. This article focuses on the latter perspective, using DTI as a way of diagnosing ASD. While the Autism Diagnostic Observation Schedule (ADOS) [7], a standardized set of tests that assess and diagnose autism spectrum disorders across age, developmental level, and language skills, is considered the gold standard for autism diagnosis, this study introduces a computer-aided algorithm that may aid reaching early-stage non-subjective diagnosis.

DTI has drawn a lot of attention over the last two decades as it allows the analysis of the structural connectivity of the brain white matter (WM) [8]. Although a lot of information could be revealed from the axonal organization, conventional MRI techniques were not capable of capturing this information due to limited resolution and contrast. Fortunately, this has been achievable using DTI, which is characterized by its diffusion anisotropy contrast that reveals information about axonal orientation. DTI is based on the diffusion of water molecules, which is easier in the direction of the axonal bundles compared to the perpendicular direction, making it feasible to determine axonal direction. In DTI, the diffusion of water molecules is measured along at least six predetermined directions, from which the diffusion along any arbitrary direction can be calculated. This is mathematically represented by a 3×3 matrix, called the diffusion tensor [9], usually interpreted graphically as an ellipsoid. Several features can be extracted from the diffusion tensor, most importantly, fractional anisotropy (FA), axial and radial diffusivity, and mean diffusivity (MD) [10]. Those measured parameters provide information about WM micro-structure and connectivity [11]. Other features derived from those measurements, such as trace, skewness, rotational invariance, and others, characterize different aspects of diffusivity in WM tracts [12].

Several studies [6], [13]–[21] have examined WM in people with ASD using DTI, comparing their WM microstructure with that of typically developed (TD) individuals. Barnea-Goraly *et al.* [6] found that certain white matter areas had reduced FA in ASD, when taking into consideration IQ, age, and gender. The white matter tracts they identified were located in brain regions known to be associated with social cognition e.g., temporoparietal junction, superior temporal sulcus, ventromedial prefrontal cortex, fusiform gyrus, and anterior cingulate gyrus. While the aforementioned study [6] did not report any ASD-related alterations in mean diffusivity, the work of Alexander *et al.* [13] found significant differences in MD as well as FA. Specifically, MD was increased in callosal white matter, while FA was reduced, for individuals with ASD as compared to TD subjects. Higher MD and radial diffusivity with reduced FA in autistic subjects was reported by [14]. Another study [15] examining the frontal lobe white matter reported lower FA values and a higher diffusion coefficient in ASD.

Vasa *et al.* [20] reviewed some of the current structural and functional connectivity ASD data to examine the ''disrupted connectivity" theory. They identified many confounding factors in the literature that could have affected the conclusions and highlighted the conflicting results. Disrupted connectivity is regarded as a key feature in the pathophysiology of autism spectrum disorder (ASD) [20], [22]. This point of view was first proposed by Belmonte *et al.* [23] in a model where reduced information transfer in the brains of ASD individuals was seen as a consequence of local overconnectivity and long-range-underconnectivity. According to the disrupted connectivity hypothesis, weaker functional connections among disparate brain regions hamper their ability to integrate complex cognitive tasks [24]. Belmonte's explanatory framework relied heavily on Brock *et al.* [25] studies suggesting the presence of underconnectivity between distant brain regions as reflected in a lack of EEG synchrony in the gamma band. The concept was further elaborated by Rippon *et al.* [26] as an ''impaired connectivity" hypothesis of autism by tying together the relevance of gamma band activity to the excitatory/inhibitory balance of cortical activity [27]–[29]. Neuropathological studies of neuronomorphometry and columnar structure give credence to the disrupted connectivity hypothesis and its possible ties to the excitatory inhibitory balance of the cerebral cortex [30]. According to researchers a shift in cell/minicolumnar size has biased brain connectivity so as to develop an ''intrahemispheric modus operandi" [30], [31]. The structural integrity of WM was examined using DTI [16], comparing ASD and TD groups with correction for age and IQ, and also without. The individuals with ASD were found to have significantly higher MD generally in cerebral and cerebellar white matter, regardless whether the correction was performed or not. The authors also noted decreased FA in ASD within the superior and inferior longitudinal fasciculi bilaterally, and in the left corona radiata; however, this decrease almost disappeared after correcting for age and IQ. From this they inferred that the kurtosis of fractional anisotropy distribution is greater in ASD. Travers *et al.* [17] presented a comprehensive review of 48 studies that were carried out from 2004 to 2012 for the purpose of studying the WM integrity of ASD using DTI. The review found consistent results among these studies in that ASD cases on average exhibited reduced WM integrity compared to TD individuals, indicated by lower FA and increased MD across multiple brain regions. The findings were more consistent in some regions with respect to others, especially in the cingulum and corpus callosum. Kuno *et al.* [21] examined correlations between DTI parameters (fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity) and scores on the Autism-spectrum Quotient (AQ). They focused on white matter tracts that were known from previous studies to be altered in obsessive-compulsive disorder (OCD) patients with autistic traits. Their results suggested that the

variations in WM features may be explained partially by autistic traits in OCD patients.

Utilization of machine learning in brain studies in general, and in DTI brain studies in specific has been around for many years; however, there are not many publications related to classification, or characterization of ASD using DTI [17], [32]. Zhang *et al.* [33] performed a whole brain white matter connectivity analysis using different classifiers, and diffusion MRI tractography to classify between ASD and TD. In [34], Payabvash et al used DTI metrics like fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) along with the structural connectome examined using edge density imaging. He used SVM, random forest (RF), neural networks (NN), and naive Bayes (NB). It is worth noting that edge density imaging is a 3D spatial embodiment of the edges of the connectomes that has been placed on the cortical and subcortical gray matter regions [35]. DTI imaging has also been utilized in classification problems other than autism like Alzheimer [36]–[38], dyslexia [39], and many other disorders, such as epilepsy [40], auditory processing disorders [41], and many other neurological disorders [42]. In one study of 40ASD, 35TD subjects, [43] showed a diagnostic predictive capability, with 80% accuracy, based on FA and MD average values per ROI. Another study that aimed to provide classification of autism, performed on 73 male subjects (41 ASD and 32 TD), used the shape of white matter tracts seeded white matter tracts seeded in the splenium of the corpus callosum to achieve an accuracy up to 75% [44]. In [19], WM connectivity was analyzed and its integrity was used in the diagnosis of autism in 38 balanced-groups of infants. While DTI-measures used for classification in previous literature includes using: raw voxel values of a predefined ROI, non-preserving dimensionality reduction of raw values using PCA, PLS, or autoencoders, or summary values of ROIs/brain areas such as average, we here introduce a novel feature representation that make use of a micro-structural correlations between different brain areas.

As concluded from similar investigations, neither the under-connectivity nor the over-connectivity of the brain hypothesis can successfully describe the deviations of the ASD population alone [20], [45]–[47]. Despite the numerous efforts to detect autism-related variations using imaging, there is no robust, effective computer aided diagnostic (CAD) system that is able to both predict a diagnosis of autism spectrum disorder and identify brain WM areas that mostly correlate with autism. This is what originated the idea of using DTI in order to develop an extensive automated diagnosis system that can help clinicians early identify ASD subjects, identify sub-types of the disorder and enable a better understanding of affected brain areas that may help develop personalized treatment plans for individuals with autism spectrum disorder.

II. METHODOLOGY

The primary objective of this work is to extract informative local white matter features for each brain area that can be used to discriminate an ASD diagnosis. Fusing the results of those local associations would help obtain an accurate global diagnostic decision per subject. The framework mainly consists of three stages: first, a preprocessing step is carried out to reduce imaging artifacts and eliminate non-brain tissues. The second stage is feature calculation, extraction, and selection, including the use of an atlas-based segmentation technique to allocate features for each area. The third stage is a classification step that is used for obtaining the final diagnosis, as well identifying specific brain areas that offer best help to differentiate ASD from neurotypical. Details of the proposed framework as well as experimental results are discussed in the next sections. Data for this experiment were obtained from the National Database for Autism Research (NDAR) [48]. Anonymized MRI scans were obtained for 263 subjects (131 females and 132 males, 124 autistic and 139 typically developed). The subjects' ages were between 8 years to 17.9 years, and they had IQs ranging between 84 and 118. A summary of the cohorts of subjects used in the study is shown on TABLE1. Data used in this study were acquired at George Washington University, with study collection ID 2021, and TABLE 2 show the acquisition parameters of the data.

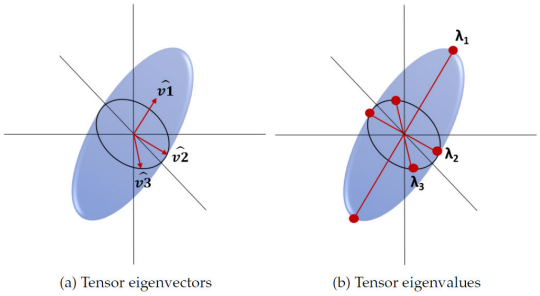

FIGURE 1. Graphical representation of diffusion tensor using the ellipsoid model using three eigenvectors that define the orientation of the ellipsoid in 3D, and three eigenvalues that define the principal axes values of the ellipsoid.

A. WHITE MATTER CONNECTIVITY ANALYSIS

For each subject, white matter was studied using diffusion tensor imaging (DTI) information. In DTI, a 3×3 diffusion tensor describes the diffusion of water within the volume of tissue contained in each voxel. To find the principal diffusion directions, the 3 eigenvalues λ_1, λ_2, and λ_3 and their corresponding eigenvectors v_1, v_2 and v_3 are calculated, where the eigenvector corresponding to the largest eigenvalue is the principle diffusion direction (i.e, diffusion across the fiber) while the other two eigenvectors correspond to the radial diffusion directions (i.e,diffusion perpendicular to the fiber) as illustrated in FIGURE 1 [49].

A special case is an isotropic medium, where the diffusion ellipsoid takes the shape of a sphere where $\lambda_1 = \lambda_2 = \lambda_3$. In the case of an anisotropic medium, the diffusion is represented as an ellipsoid as shown pointing in the v_1 direction of λ_1. There are six output features obtained from DTI

that are the most commonly used anisotropy measurements describing white matter connectivity:

1) Fractional Anisotropy (FA): The most widely used measurement of anisotropy, a scalar value between 0 and 1 that determines the diffusion integrity. As FA approaches 0, the diffusion is considered to be isotropic while higher values mean that the diffusion tends to be in a uniform direction (i.e., the principal eigenvector direction) [49], [50].
2) Mean diffusivity (MD): Average diffusivity within a voxel, integrated over all directions, $\text{MD} = \frac{1}{3}(\lambda_1 + \lambda_2 + \lambda_3)$.
3) Axial diffusivity (AD): Diffusivity in the direction of the major axis of the diffusion ellipsoid, $\text{AD} = \lambda_1$.
4) , 5) Radial diffusivities λ_2 *and* λ_3: in the direction of the minor axes of the diffusion ellipsoid.
6) Skewness: a third-order measurement characterizing the shape (oblate or prolate) of the diffusion tensor, which is not captured by FA or other lower order measurements [12]. $Skewness = \frac{(\lambda_1 - MD)^3 + (\lambda_2 - MD)^3 + (\lambda_3 - MD)^3}{3}$.

In the present study, FSL toolbox https://fsl.fmrib.ox.ac.uk was used for pre-processing and DTI computation. Pre-processing steps involves conversion from DICOM to NIfTI, brain extraction to remove skull and non-brain tissues, and performing eddy current correction that aims to reduce distortion induced by eddy currents and correct for motion artifacts. The brain extraction using *BET* algorithm [51], [52] and eddy current correction [53] using *eddy_correct* tool were applied to diffusion weighted (DW) volumes prior to calculating the diffusion tensor using *DTIFIT*.

The calculated features are then aggregated over the 48 local regions defined by Johns Hopkins WM atlas parcellation [54] using DTI-TK software. The atlas-based segmentation task is elaborated in the next subsection. Finally, the rest of the proposed algorithm is implemented in Matlab.

1) BRAIN PARCELLATION INTO LOCAL BRAIN AREAS

After calculating the above metrics at each voxel, it is useful to aggregate them by region according to an appropriate brain parcellation. An atlas-based segmentation approach is adopted, where we treat the area's segmentation problem as a registration task. In this step, the Johns Hopkins WM atlas [54] along with its labeled areas are used. John Hopkins is an ICBM coordinate-based WM atlas which defines 48 brain areas that were hand segmented from 81 different subjects. A two-step registration from the MNI atlas space to each subject's space is performed: rigid followed by affine transformation. Rigid registration aims to find a linear transformation that does not change size or shape of object, thus providing a good initial estimate for affine registration. Affine registration improves upon the found alignment by finding a more general linear transformation that allows object size and shape to be altered. The two-step registration is performed using DTI-TK software [55], which supports interoperability

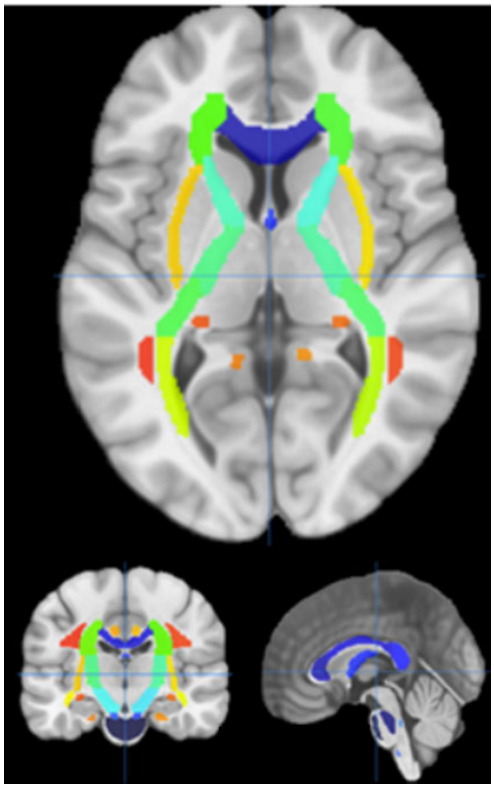

FIGURE 2. Illustration of Labeled WM areas of John Hopkins Atlas, where each color identifies different WM area.

with FSL. After atlas-subject registration, the found transformation is applied to JHU atlas labels, providing WM areas masks for each subject. Thus, we can get local features for each WM area that are used at the local classification level. FIGURE 2 shows an example of the labeled brain regions visualization. FIGURE 3 shows the entire diagnosis pipeline. The main advantage of this technique is that it is scalable, automated, and has high accuracy.

2) FEATURE SELECTION

The above mentioned procedures provide six feature volumes (FA, MD, λ_1, λ_2, λ_3, and Skewness), per each subject. All of those are raw per-voxel values for each brain area, thus some feature vectors are tens of thousand of values in length per area. To provide a compact representation, we calculate a short summary statistics vectors (mean [μ], standard deviation [σ], and skewness [$E(x-\mu)^3/\sigma^3$]) for each area. Then, we concatenate those summary statistics resulting in a feature vector of length 18 per each area (6 feature types $\times$ 3 summary statistic vector length). Instead of using those direct features, we derive new ones capturing the implicit relationships between different brain areas' values, calculated as the correlation between the feature vectors of each two areas. We further reduce this large feature space (48×48 per subject), relative to the sample size (263 subjects), by extracting only the important discriminatory features, to build our diagnosis algorithm. For this purpose,

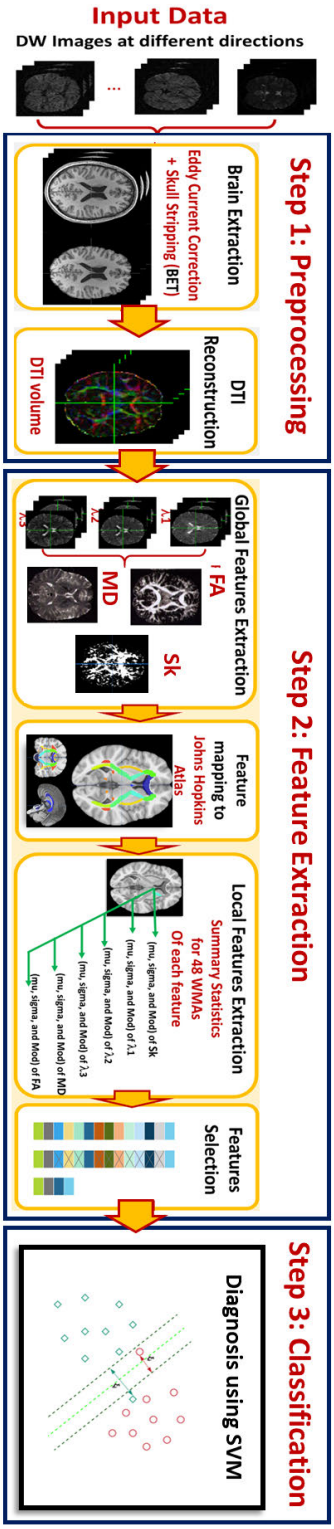

FIGURE 3. DTI experiment pipeline, where the brain is extracted, preprocessed, features calculated, atlas based segmentation performed, and selected features are incorporated for final classifiers.

we used a simple filtering method known as the signal to noise ratio (s2n) filter [56]. In this method, we rank each feature based on a score representing the ratio between the absolute difference of the means of the two classes and their variance,

Algorithm 1 DTI-Based ASD Diagnosis System

∀ **dwMRI subject's data**:
1. Arrange input files: convert DICOMs to NII, check for errors, check bval and bvec files.
2. run preprocessing modules:
   i) Eddy Current Correction.
   ii) Apply brain mask generated by running Brain Extraction Tool (BET).
3. Feature Calculations:
   i) Use FSL to calculate DTI Tensor, scale units, calculate λ_1,λ_2,λ_3,FA,MD, sk volumes
   ii) Register DTI MNI space IIT Human Brain Atlas to each subject using DTI-TK
   iii) Apply resulted transformation on the JHU atlas labels
   iv) Use registered labels to extract feature per each WM area
   v) Calculate summary statistics ($\mu, \sigma, Skwns$) for each area for each feature (λ_1,λ_2,λ_3,FA,MD, sk), rank feature values across the different 48 brain areas, get a concatenated feature vector (3*6).
   vi) Calculate correlations between feature vectors of each two areas
   vii) Use s2n filter to rank correlation-features
3. Classification:
   i) iterate on n from 1 to 250.
   ii) Feed first n ranked ordered feature for all subjects to an SVM classifier
   iii) Give a final diagnosis for each subject, whether TD or ASD
End.

given by

$$s2n(X_i, Y) = \frac{abs(\mu(y_+) - \mu(y_-))}{var(y_+) + var(y_-)} \quad (1)$$

where X_i is the feature vector, and Y is class label, $\mu(y_+)$ is the mean value for class y_+ vectors, and $var(y_+)$ is the variance for this class. FIGURE 4 illustrates the adopted feature selection technique. Then, we use only the highest-ranking features in next steps.

B. ASD DIAGNOSIS

Having pairwise correlated the DTI metrics of WM regions, each of the resulting features, i.e. each region pair, was used separately to distinguish between ASD and TD subjects on the global level. The contribution to diganostic accuracy of each feature incorporated into the classifier is shown, highlighting those that were most relevant to ASD. A number of classifiers from diverse classifier algorithms were tested, including Support Vector Machine, k-Nearest Neighbor (KNN), decision trees, and neural networks (NN). Experiments found the best performance in terms of cross-validated accuracy and processing time for Support Vector Machine (SVM). Linear SVM-classifiers were used

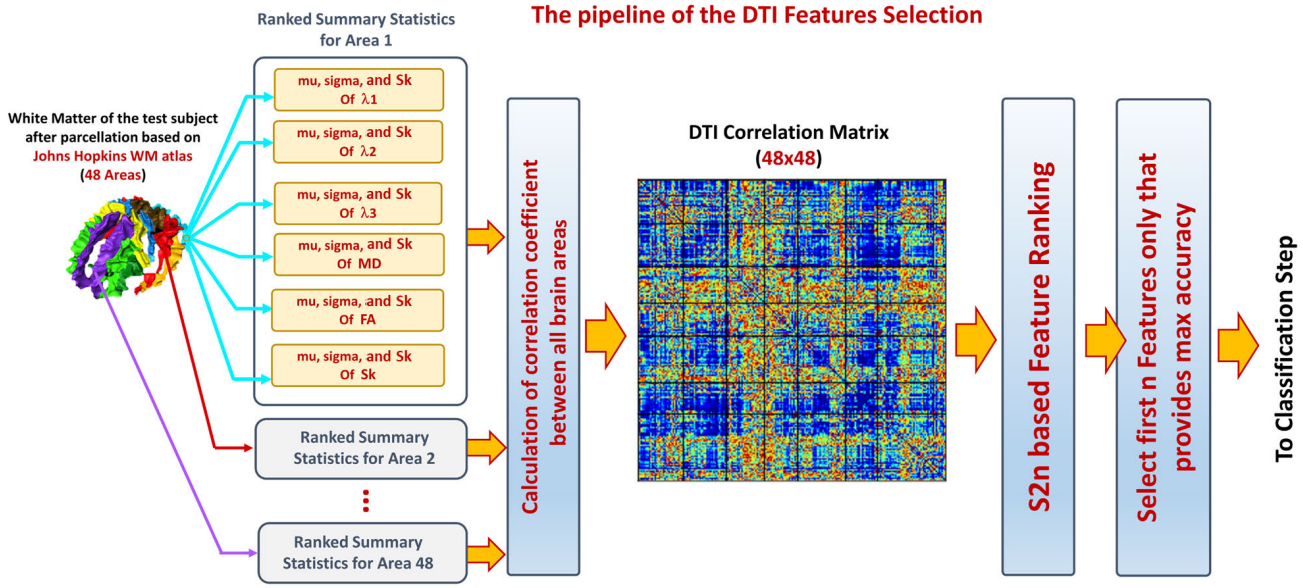

FIGURE 4. DTI feature extraction procedure.

TABLE 1. Summary of the study cohorts. TD: Typically developed (control) subjects. ADOS CSS: Calibrated Severity Score, independent of age and language ability. S.A.: Social affect score, R.R.B: Repetitive and restricted behaviors score.

	ASD (N = 124)		TD (N = 139)	
Number of Males/Females	M = 66, F = 58		M = 66, F= 73	
AGE (months)	mean	std	mean	std
Male (N = 132)	150.697	36.57	155.682	33.24
Female (N = 131)	155.621	32.47	153.219	37.64
ADOS CSS	median	Range		
S.A.	6.77	1-10		
R.R.B	6.68	1-10		
CSS total	6.74	1-10		

TABLE 2. Acquisition parameters of DTI data used.

Description	Value
Study collection id	2021
Image description	DTI
Original Image file format	DICOM
Equipment Manufacturer	Siemens
Equipment Type/name	Magnetom TrioTim
Aquisition/analysis Software Versions	syngo MR B17
Magnetic field strength	3T
Scanning Sequence	Echo Planar
Sequence Variant	SK: segmented k-space, SP: Spoiled
Repetition Time	9000
Echo Time (seconds)	93
Flip angle	90
Acquisition matrix	96x96
Patient position	Isocenter
Photometric interpretation	RGB
Receive coil name	auto
Transmit coil name	auto - Body
Resolution [1] X dimension [Millimeters]	190
Resolution [2] Y dimension [Millimeters]	190
Resolution [3] Z dimension [Millimeters]	120
Number of Slices	64+1
Slice thickness [Millimeters]	2
Orientation	Axial
collection_title	Multimodal Developmental Neurogenetics of Females with ASD

on each classification level, taking correlation features as inputs and producing a normalized score (0–1) indicating the confidence that a subject is autistic given the WM areas for which information was provided. Of course, not all areas are expected to contribute significantly to the decision between ASD and TD, so only first n features are used for classification, where n is determined empirically. FIGURE 3 shows the pipeline of the entire diagnostic framework.

III. EXPERIMENTAL RESULTS

Data for this experiment were obtained from the National Database for Autism Research (NDAR) [48]. De-identified diffusion MRI data were accessed, comprising 263 subjects (131 females and 132 males), each marked with a globally unique identifier (GUID). Of these, 124 had a diagnosis of ASD, confirmed with ADOS, while the other 139 individuals did not have any pervasive developmental disorder. The subjects were between 8 and 18 years of age at time of MRI acquisition, and their Wechsler full-scale IQs ranged from 84 to 118. A summary of the cohort statistics is provided on TABLE 1. Data used in this study were acquired at George Washington University, with study collection ID 2021, and TABLE 2 show the acquisition parameters of the data. GUIDs for all subjects used in this study are provided as a supplemental materials.

To ensure system robustness, we used leave-one-subject-out (LOSO) cross-validation at all runs. For each WM area, overall accuracy, sensitivity, and specificity were calculated.

Obtaining a subject's global diagnostic decision is a two step procedure. First, features are ranked based on the s2n score, then iteratively first n is fed to next step, with n starting from 1 to 250. n is selected as the n features providing highest accuracy. Selected features are concatenated, and SVM classifiers are used to make a decision of ASD

TABLE 3. Top ten pairs of white matter areas whose feature-vector correlations provides separability with highest rank according to s2n filter. Regions represented in both hemispheres are annotated with L (left) or R (right) if only one hemisphere is involved, or with B (bilateral) otherwise.

Rank	Area 1	Area 2
1	Superior longitudinal fasciculus R	Anterior corona radiata R
2	Body of corpus callosum	Genu of corpus callosum
3	Superior longitudinal fasciculus R	Sagittal stratum
4	Tapetum L	Middle cerebellar peduncle
5	Splenium of corpus callosum	Middle cerebellar peduncle
6	External capsule L	Middle cerebellar peduncle
7	Cingulum L	Corticospinal tract R
8	Stria terminalis R	Superior corona radiata L
9–10	Superior longitudinal fasciculus L	Posterior corona radiata B

or TD based on the concatenated feature vector, providing a single global decision per subject. The optimal classifier achieved overall diagnostic accuracy of 73%, 70% sensitivity, and 76% specificity. This performance was achieved using $n = 79$ correlations. The most significant of these region pairs are listed in TABLE 3.

IV. DISCUSSION

The most important regional correlations for distinguishing ASD from control (TABLE 3) are a diverse group, yet they fall into five categories. First is the middle cerebellar peduncle (MCP) as it correlates with the splenium of the corpus callosum, the left external capsule (EC), and the left tapetum. The uncinate fasciculus is a fiber pathway through the EC, which links the ventral frontal cortex, in particular Brodmann areas 11 and 47, with the temporal pole [57]. Commissural fibers of the left temporal pole, and of the temporal lobe in general, pass through the left tapetum on their way to or from the splenium. The MCP on the other hand carries signals from the cerebral cortex and subcortical regions, via the pontine nuclei, into the cerebellar cortex.

Next are correlations between the superior longitudinal fasciculus (SLF) on the right hemisphere with ipsilateral sagittal striatum (SS) and anterior corona radiata (CR), and between SLF in the left hemisphere with bilateral posterior CR. The SLF is a bidirectional pathway along the anterior-posterior direction through which different lobes communicate with each other [58]. Thalamocortical fibers pass through the SS and CR, where they intermingle with callosal axons [59]. In this category as well as the first, we see in ASD a difference in the microstructure of cortico-cortical pathways *relative to* pathways linking the cerebral cortex with outside regions.

Output from the left motor cortex passes through the corticospinal tract on the opposite side. Communication between left motor and premotor areas meanwhile makes use of pathways through the left cingulum. The middle segment of the cingulum would be involved in particular; however, the atlas used in this study does not parcellate the cingulum further, so we were only able to identify altered correlation between left cingulum as a whole and right corticospinal tract. Still, this once again suggests changes in a cortical area's connectivity with elsewhere in the cortex *vis-à-vis* regions outside the cortex.

The superior CR contains sensorimotor fibers of the posterior frontal/anterior parietal cortex. The microstructure of this region by itself has been found to differ between ASD and typically developing children [60]. The stria terminalis contains efferent fibers from the amygdala, which terminate in several nuclei of the hypothalamus and regulate the stress response. We might hypothesize that the increased stress response seen in ASD [61] is normal hypothalamic activation triggered by abnormal sensory processing. While the differences in the superior CR found by Pryweller and colleagues [60] were more pronounced in the left hemisphere, statistical testing did not find this significant. Nor was there any significant distinction between superior CR and other sensory processing pathways they investigated; all showed increased apparent diffusivity in ASD. It is not clear why in our study left superior CR, relative to stria terminalis, particularly stood out.

Differences in the microstructure of genu and body of the corpus callosum relative to each other are harder to interpret, given that they are complementary parts of the same structure, containing commissural fibers from distinct regions of the cortex. It may be of significance that the sections of the corpus callosum develop at different gestational ages. The axons forming the genu grow first, starting in the twelfth or thirteenth week of gestation, followed by the body and splenium in anterior-posterior order, and finally the rostrum [62]. Could this be a clue to pinpointing the developmental stage at which the propensity for developing ASD originates?

There remain several challenges to address and potential enhancements to be made with regard to this system. In particular, while the LOSO approach is an efficient means to maximize the data available for machine learning and still obtain reasonable estimates of classification accuracy, testing on an independent data set is necessary to demonstrate the classifier's ability to generalize. It is important to point out that the correlation matrices were provided for statistical dependencies between disparate brain area regardless of any underlying anatomical link or connectivity. Thus, analysis of clinical and cognitive-behavioral data, beyond the diagnosis of ASD or non-ASD, is needed to map the affected brain to specific ASD symptoms. The differences in regional correlations we have found so far will be useful for constructing testable hypotheses in that regard. Though many registration tools were tested on the bulk of the data set, a WM area parcellation tailored to the individual (e.g., using tractography) could lead to better feature extraction and hence improved performance.

The next step for our CAD implementation will be to incorporate different imaging modalities, such as structural or functional MRI. In this way, the CAD system will be able to relate WM microstructure with brain shape (e.g., cortical folding), and structural connectivity with functional connectivity. Expanding the feature space in this way might enhance classification accuracy and provide better understanding of symptoms and personalized diagnosis.

V. CONCLUSION

In summary, the proposed diagnosis framework achieved various goals. The classifier's performance, with a moderately large sample size of 263 subjects, is in the upper range of those DTI-based studies reported in the literature. Beside accomplishing a high diagnostic accuracy, it has identified pairs of white matter areas that exhibit relative differences in ASD, as opposed to considering microstructural changes within contiguous WM regions. This provides for another way of looking at ASD as a disorder of brain connectivity, and should in turn lead to a better understanding of an autistic individuals' behavior and predictability of disorder development for those at risk. In addition, the feature selection approach used in our system is scalable, in that additional imaging modalities or even non-image data could be incorporated into the feature space, and their contribution to the classification could be considered separately or jointly.

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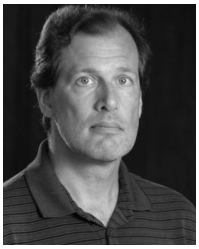

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