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APPROACHES TO COMPUTER AIDED DIAGNOSIS OF AUTISM SPECTRUM DISORDER

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Abstract: *Autism is a broad neurodevelopmental disorder affecting the memory, behavior, emotion, learning ability, and communication of an individual. The computer aided diagnosis (CAD) of Autism Spectrum Disorder (ASD) has been gaining interest in the scientific community in the recent years, aiming to achieve early detection that may allow to apply therapeutic or palliative treatments from an early age. In this paper we gather some of the approaches that have been reported in the recent literature. Some approaches deal with behavioral characterizations, while the majority of approaches deal with the analysis of neural activity and brain connectivity in some way or another. Most recent studies are focused on the detection of brain functional connectivity anomalies using specific signals such as electroencephalographic (EEG) recordings or functional magnetic resonance imaging (fMRI). The publication of large public repositories of data is boosting research in this topic, promising to find robust biomarkers and discrimination models for robust CAD systems.*

Keywords: *Autism Spectrum Disorder, Biomarkers, Computer Aided Diagnosis, Magnetic Resonance Imaging, Machine Learning.*

1. INTRODUCTION [1]

Autism is a type of neurodevelopmental disorder affecting the memory, behavior, emotion, learning ability, and communication of an individual. Autism spectrum disorder (ASD), aka autism spectrum condition (ASC), is a chronic inhabilitating cognitive impairment that takes a wide variety of forms, hence the use of the term "spectrum", and has a high prevalence in the general population, with a neat imbalance in distribution towards the male gender. A normative study on brain cortical structure modeled by a probabilistic predictive model concluded that there is some indication that sexual-related characteristics of the brain are highly correlated with ASD [6].

Computer aided diagnosis (CAD) aims to help the clinical practitioner to achieve early and accurate diagnosis of ASC in order to try to apply early treatments hoping to improve the child's condition in some way [11, 25, 26, 28, 30, 35]. In this paper we will not discuss the clinical standard protocols and practices applied to obtain a diagnosis.

A search in Pubmed using the terms "computer aided diagnosis autism" resulted in 285 references. The peak interest seems to be in year 2012, but a steady flow of papers is appearing since then dealing with the problem of devising CAD tools for ASD diagnosis coming from a diversity of bio-information sources. Though there have been attempts to build CAD rule based expert systems [23] relying only on qualitative information, such as parents questionnaires, most of the current works are directed towards the identification of biomarkers that may support the application of machine learning approaches to build the CAD system, such as the selection of microarray expression data [13, 18, 19], or the detection of specific metabolites that are related to ASD [22]. Imaging information, such as magnetic resonance imaging (MRI) of diverse modalities has a big potential to provide such biomarkers. For instance, structural MRI has provided evidence of atypical brain lateralization of subject with ASC [10] in a cohort of 67 ASC subjects and 69 neurotypical subjects with matching IQ and relevant personal characteristics. Most of the CAD or biomarker identification approaches are developed on small local datasets, but recent trends aim to use multi-center information in order to achieve more robust classification results [15, 33], such as the Autism Brain Imaging Data Exchange (ABIDE) repository (http://fcon_1000.projects.nitrc.org/indi/abide/index.html), which contains information from more than one thousand ASD patients and healthy controls, or the UK Medical Research Council Autism Imaging Multicentre Study (MRC AIMS). It has been argued, however, that inter-site variability seriously impedes the data analysis [24]. After removing inter-center variability predictive classification results are reported close to random noise, enforcing the conclusion that more specific differential diagnostic tools are needed because of the actual heterogeneity of the brain structures.

The contents of the paper are as follow: Section 2 presents CAD behavior measurement based approaches.

Section 3 presents some approaches using EEG data. Section 4 presents approaches based on MRI data, which

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is the most exploited approach nowadays. Finally, Section 5 gives some concluding remarks.

2 BEHAVIOR MEASUREMENT BASED APPROACHES.

Some approaches use behavioral information measured by computer vision or another sensing technique. For instance, in [20] authors propose the measurement using computer vision of the imitation response of ASC children versus neurotypical children to discriminate them. Another non intrusive approach to discriminate ASC children uses the inertial information of a smart tablet [4]. The authors find definitive patterns of motion that are compatible with the ASC clinical characterization, larger and faster motions, stronger forces at contact, with more distal use of space. Another approach uses the Kinect V2 sensor in order to measure the motions of the subjects and try to detect stereotypical motor reactions which are the hallmark of autism in clinical diagnosis processes. The experiments reported with motion captured from professional actors promised that this detection can be achieved with great probability [16].

3 EEG BASED DETECTION.

It has been established empirically the possibility to discriminate between neurotypical children and ASD children on the basis of carefully crafted analysis of their brain activity recorded by Electroencephalographic (EEG) sensors [5]. The analysis requires sophisticated time series analysis, including features computed from non-linear chaotic time series analysis and time frequency decomposition. The fractal dimension together with the entropy are reported in this review as discriminant features. A computational pipeline consisting in the application of a wavelet decomposition, following by the computation of entropy features from each EEG sub-band and finally an artificial neural network (ANN) classifier has been tested with good classification results [8]. Another approach, uses the self-organizing map (SOM) for feature extraction of EEG signal, and tests a number of conventional classifiers, achieving a high accuracy in classification of ASD versus neurotypical children [12]. However, such works are removed from the clinical practice because they do not provide adequate explanation relating the discrimination results to the mechanisms underlying them. They are in a sense blind methods, or black boxes. Clinically oriented studies try to come up with explanations that involve anomalies in the functionality of the brain, such as effects of brain connectivity. A recent systematic review on connectivity analysis based on EEG and magnetoencephalography (MEG) [29] has found systematic long-range underconnectivity in ASD, while analysis of local connectivity does not provide definitive conclusions.

4 MRI BASED DETECTION.

Another track for research into the existence of anomalies in brain functionality connectivity is the use of various modalities of magnetic resonance imaging (MRI), namely structural (T1-weighted) MRI, resting state functional MRI (rs-fMRI) and diffusion weighted imaging (DWI), and magnetic resonance spectroscopy (MRS) are the most relevant modalities to identify ASD biomarkers [21]. Biomarker identification aims to detect brain regions, connections or biochemical signatures that show significant differences between ASD and neurotypical populations. CAD goes one step further, it produces a decision on the diagnosis that can be used by the clinical practitioner with some confidence. CAD systems require sophisticated machine learning tools, such as multiview multitask ensembles of classifiers [33]. Image biomarker findings are quite diverse [21]. Structural MRI findings using voxel based differences are sometimes contradictory and inconsistent, and heavily dependent on the technique used and the age of subjects, though some increase in gray matter and white matter volume was consistently reported, as well as corpus callosum decrease in volume. Morphological differences in thalamus and striatum have been also reported using structural features [31]. Increased cortical thickness was reported for ASD in the range between 6 years and adolescence [17], with differences decreasing towards adulthood. Other authors report significant differences in temporoparietal regions [38]. One of the questions raised is whether the differences in measurements found in older children may be due to the actual ASD effects or the years of social dysfunction. Hence, the current preferences of researchers on biomarkers is to do the observations in very early ages, even toddlers. Tractography analysis based on fractional anisotropy coefficients extracted from DWI data have shown consistent degradation of main neural tracts, pointing to a degradation of brain connectivity. The analysis of functional connectivity based on rs-fMRI data has found also many incoherent or contradictory results heavily dependent on the actual seed regions selected for connectivity computation. The accepted conclusion so far is that there is some form of compensation between reduced long-range connectivity and increased short-range connectivity. The functional parcellation of the insula allowed to find differences of insula functional connectivity between ASD and neurotypical subjects [37].

The spatial shifting of resting state networks, such as the default mode network, has been also tested as a biomarker for ASD [27]. The parcellation of the brain activity into intrinsic connectivity networks allowed to assess their spatial variability and its discriminant power, ASD showed greater spatial variability. These results help to harmonize the contradictory findings of underconnectivity and overconnectivity in several studies [2]. Increase in intrasubject variability brain connectivity in time, due to diverse factors such as caffeine intake between sessions, has been found a potential biomarker for ASD [9]. Connectivity of the thalamus cortex has been studied by rs-fMRI brain networks and anatomical connectivity computed by diffusion weighted imaging tractography [1] finding diverse patterns of underconnectivity. The study of brain connectivity in toddlers comparing ASD with other developmental disorders has bee reported using DWI and streamlined tractography [7]. Over an anatomical parcellation of the brain, the neural pathways between them were extracted, and the connectivity strength between brain regions was estimated. The results point to overconnectivity in ASD

toddlers versus other developmental disorders. On other effort, the connectivity between the cerebellum and the temporoparietal junction was analyzed in detail using both independent component analysis and seed based connectivity analysis [14] finding perturbed input to the termporal-parietal regions from the cerebelar areas.

Many CAD systems proceed by computing first some kind of features which are then input to some conventional classifier, such as linear support vector machines (SVM). A tensor based approach to estimate connectivity in rs-fMRI is proposed in [39] that it is able to extract both the connectome representation and the dynamic functional connectivity for each subject finding discriminant effects on the putamen connectivity for ASD subjects. Fine temporal analysis of the rs-fMRI time series, by clustering them into short time intervals that may be shared between brain regions, allows more precise classification [34, 40]. On the other hand, structural features of brain cortex were used by random forest classifier to produce reliable predictions in toddlers [36].

Deep learning is having also a definitive impact in the recent attempts to construct CAD systems. For instance, Deep Belief Networks have been reported [3] to achieve ASD children discrimination fusing structural MRI imaging data and rs-fMRI data. Another approach [32] uses sparse autoencoders to extract feature filters from structural MRI, which are applied to the 3D structural MRI by a convolution neural network for feature extraction. A linear decomposition by independent component analysis is applied to extract rs-fMRI connectivity features after appropriate signal bandpass. Structural and functional features are finally entered to a linear support vector machine (SVM) classifier. However, deep learning approaches are blind, in the sense that no biological information is provided by CAD system, so there is no explanation that may lead the clinical practice to find treatments.

5 CONCLUDING REMARKS

Computer aided diagnosis (CAD) systems for ASD are currently a focus of research, because they may provide early detection leading to improved treatment. CAD systems provide the clinical practitioner with a recommendation of the diagnosis, which may (or may not) be based on accepted biomarkers. Blind CAD systems are not easily accepted because the medical staff requires understanding the recommendation from a causality point of view. Therefore, future efforts must emphasize explainability in order to get acceptance in the medical community.

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