Predicting symptom severity in autism spectrum disorder based on cortical thickness measures in agglomerative data

Elaheh Moradi[a,1], Budhachandra Khundrakpam[b], John D. Lewis[b], Alan C. Evans[b], Jussi Tohka[c,d,*]

[a] Department of Signal Processing, Tampere University of Technology, Tampere, Finland
[b] McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Canada
[c] Department of Bioengineering and Aerospace Engineering, Universidad Carlos III de Madrid, Avd. de la Universidad, 30, 28911, Leganes, Spain
[d] Instituto de Investigacion Sanitaria Gregorio Marañon, Madrid, Spain

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ABSTRACT

Machine learning approaches have been widely used for the identification of neuropathology from neuroimaging data. However, these approaches require large samples and suffer from the challenges associated with multi-site, multi-protocol data. We propose a novel approach to address these challenges, and demonstrate its usefulness with the Autism Brain Imaging Data Exchange (ABIDE) database. We predict symptom severity based on cortical thickness measurements from 156 individuals with autism spectrum disorder (ASD) from four different sites. The proposed approach consists of two main stages: a domain adaptation stage using partial least squares regression to maximize the consistency of imaging data across sites; and a learning stage combining support vector regression for regional prediction of severity with elastic-net penalized linear regression for integrating regional predictions into a whole-brain severity prediction. The proposed method performed markedly better than simpler alternatives, better with multi-site than single-site data, and resulted in a considerably higher cross-validated correlation score than has previously been reported in the literature for multi-site data. This demonstration of the utility of the proposed approach for detecting structural brain abnormalities in ASD from the multi-site, multi-protocol ABIDE dataset indicates the potential of designing machine learning methods to meet the challenges of agglomerative data.

1. Introduction

Autism Spectrum Disorder (ASD) is a developmental disorder characterized by impairments in social interaction and communication, restricted interests, and repetitive patterns of behavior (Lord and Jones, 2012; Wing, 1997; Gillberg, 1993). The definition admits substantial behavioral heterogeneity (Georgiades et al., 2013); ASD is, in fact, a family of developmental disorders with unique, but related, phenotypes, with a variety of genetic associations (Devlin and Scherer, 2012). Moreover, ASDs are developmental disorders, and the behavioral abnormalities evolve over time (Gotham et al., 2012; Szatmari et al., 2015), adding to the apparent heterogeneity. This large behavioral heterogeneity appears to be paralleled by a wide array of neuroanatomical abnormalities, which also evolve over development (Zielinski et al., 2014; Wolff et al., 2014). Almost every brain region has been implicated in autism, including subcortical (Jacobson et al., 1988; Cerliani et al., 2015) and cerebellar regions (Bauman, 1991; Fatemi et al., 2002), gray-matter and white-matter (Barnea-Goraly et al., 2004; Rojas et al., 2006), and regions of all lobes of the cerebrum (Zilbovicius et al., 2000; Courchesne et al., 2011; Lewis et al., 2013, 2014). Indeed, the neuroanatomical heterogeneity is so great that replication of results across studies is rare. The inconsistencies in findings are likely primarily due to the small sample sizes used in most studies, in combination with the large behavioral heterogeneity, as well as measurement related differences (Auzias et al., 2014, 2016; Castrillon et al., 2014). Thus, there is an urgent need for larger sample sizes, if we are to discover clinically useful information (Amaral et al., 2008; Auzias et al., 2014, 2016; Lefebvre et al., 2015). Large samples may allow the extraction of core neuroanatomical abnormalities from the noise introduced by the heterogeneity of the disorder. Such abnormalities could serve as biomarkers, and could provide insight into the causes of the disorder, and potential interventions.

However, datasets collected by a single site are not sufficient in size to achieve such goals (albeit making exact claims about the required

dataset size is a complex matter and depends on the goals of study (Button et al., 2013)). Further, there are limited publicly available data from multi-site studies utilizing a single scanner type with the same acquisition protocol across sites. But, so-called 'big data' has come to neuroscience, including for the study of ASD. There are currently multiple initiatives to bring together neuroimaging data from multiple sites, acquired on multiple types of scanners, and with differing protocols. The Autism Brain Imaging Data Exchange (ABIDE)[2] is one such initiative (Di Martino et al., 2014). ABIDE provides previously collected datasets composed of both MRI data and phenotypic information from 16 different international sites for over 1100 individuals, approximately half of whom are typically developing (TD) and half have been diagnosed with ASD. This sample size, which is more than an order of magnitude larger than that used in most single-site studies, provides the power needed to identify neuroanatomical abnormalities related to ASD. But, the multi-site, multi-protocol aspect of the data introduces additional heterogeneity. Indeed, previous studies using the ABIDE data have shown that acquisition site has significant effects on basic image properties (Nielsen et al., 2013; Castrillon et al., 2014). This further exacerbates the problem of identification of core neuroanatomical abnormalities in this extremely heterogeneous data. The between-site heterogeneity constitutes the main technical challenge in the current work (Auzias et al., 2014), and the solution that we offer is a contribution applicable not only to the ABIDE dataset, but to any neuroimaging data agglomeration.

The solution to the problem lies in finding a new common space within different datasets for reduction of between-site variation. Techniques for achieving this are often referred to as *domain adaptation* (Jiang, 2008; Pan and Yang, 2010). Domain adaptation is a new branch of machine learning techniques that seeks to improve the similarity of the data from different sources with mismatched distributions. We utilize these domain adaptation machine learning algorithms to address the problem that arises in the situation where the data distribution changes across different acquisition sites. We apply this approach to the ABIDE data to identify neuroanatomical abnormalities associated with symptom severity in ASD. Between-sites variance in neuroimaging studies is commonly handled by regressing out the site identity from the imaging data in a voxel-wise manner before performing analysis (Gupta et al., 2015) and similar methods have been adapted for machine learning analysis with limited success (Kostro et al., 2014). Instead, here we propose a novel approach for reducing between-sites variability by projecting data from different sites into a new, common space in a way that effectively reduces nuisance variation between the data from different sites. The current approach for dealing with the site effect is novel in the context of multi-site imaging studies, and for the estimation of severity scores in ASD patients.

The great majority of ASD studies have focused on identifying group differences between typically developing individuals and those with ASD, or conversely, training classifiers to distinguish between these groups (Ecker et al., 2010; Nielsen et al., 2013; Wang et al., 2015). But, perhaps the largest source of heterogeneity is associated with the severity of the disorder. In fact, both individuals with ASD as well as those deemed to be typically developing display a wide range of symptoms of autism in a variety of behaviors. This variability may mask neural abnormalities associated with these symptoms, and limit the success of attempts to classify an individual based on their neuroimaging data. Approaches which relate dimensional measures of symptoms to measures of neuroanatomy appear more useful than those which aim only to identify abnormalities associated with a diagnosis of ASD (Sato et al., 2013; Schumann et al., 2009). Thus, in this work we take this latter approach. We design a model to estimate symptom severity scores derived from the Autism Diagnostic Observation Schedule (ADOS) from cortical thickness measurements.

We are motivated by evidence that local cortical thickness measures provide an index of the maturation of cortex and cortico-cortical connectivity (Shaw et al., 2008; Raznahan et al., 2011), and that ASD may be characterized by delayed maturation (Webb et al., 2011; Johnson et al., 2015).

Our proposed method for estimation of the severity score consists of two main stages: a domain adaptation stage that uses partial least squares regression (PLS) with sites as response variable, and the learning stage which consists of the combination of two different regression methods, i.e. support vector regression (SVR) and elastic-net penalized linear regression (LR). We evaluate the reliability of the model across a multisite dataset without standardization of the acquisition protocol across sites, and the effect of each part of the algorithm.

2. Materials and methods

2.1. ABIDE data

The data used in this study were from the ABIDE dataset (Di Martino et al., 2014). ABIDE is a publicly available dataset that involved 16 international sites, from 532 individuals with ASD and 573 typical controls, yielding 1112 datasets composed of MRI (functional and structural) and phenotypic information for each subject. The sequence parameters as well as type of scanner varied across sites, though all data were collected with 3 T scanners. The scan procedures and parameters are described on the ABIDE website.

2.2. Image preprocessing

The T1-weighted volumes were processed with CIVET, a fully automated structural image analysis pipeline developed at the Montreal Neurological Institute. CIVET corrects intensity non-uniformities using N3 (Sled et al., 1998); aligns the input volumes to the Talairach-like ICBM-152-nl template (Collins et al., 1994); classifies the image into white matter, gray matter, cerebrospinal fluid, and background (Zijdenbos et al., 2002; Tohka et al., 2004); extracts the white-matter and pial surfaces (Kim et al., 2005); and warps these to a common surface template (Lyttelton et al., 2007). Cortical thickness (CT) is measured in native space using the linked distance between the two surfaces at 81,924 vertices. The thickness map was then blurred to impose a normal distribution on the corticometric data, and to increase the signal to noise ratio; a 30-millimeter full width at half maximum surface-based diffusion smoothing kernel was used.

Quality control (QC) of the CIVET results was performed by two independent reviewers. Data with artifacts due to motion, low signal to noise ratio, hyperintensities from blood vessels, or poor placement of the gray or white matter (GM and WM) surfaces for any reason were excluded. 215 subjects with ASD were excluded in the QC.

2.3. Subjects

After image preprocessing and the QC, the number of ASD subjects reduced from 532 to 317 from 16 different sites. Next, we excluded ASD subjects with missing ADOS total and module information and then we included only subjects from sites containing at least 20 subjects. The remaining 156 subjects were from 4 different sites (NYU, PITT, TRINITY, USM) which were used for estimating severity score. Details of the characteristics of the ABIDE samples used in this work are presented in Table 1. The subject IDs of the included subjects can be found in the supplement.

2.4. Severity score

This work studies the relation between cortical thickness and measures derived from the Autism Diagnostic Observation Schedule

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