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Inter-regional cortical thickness correlations are associated with autistic symptoms: A machine-learning approach

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ABSTRACT

The investigation of neural substrates of autism spectrum disorder using neuroimaging has been the focus of recent literature. In addition, machine-learning approaches have also been used to extract relevant information from neuroimaging data. There are only few studies directly exploring the inter-regional structural relationships to identify and characterize neuropsychiatric disorders. In this study, we concentrate on addressing two issues: (i) a novel approach to extract individual subject features from inter-regional thickness correlations based on structural magnetic resonance imaging (MRI); (ii) using these features in a machine-learning framework to obtain individual subject prediction of a severity scores based on neurobiological criteria rather than behavioral information. In a sample of 82 autistic patients, we have shown that structural covariances among several brain regions are associated with the presence of the autistic symptoms. In addition, we also demonstrated that structural relationships from the left hemisphere are more relevant than the ones from the right. Finally, we identified several brain areas containing relevant information, such as frontal and temporal regions. This study provides evidence for the usefulness of this new tool to characterize neuropsychiatric disorders.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impaired social communication, social reciprocity, and repetitive/stereotypic behavior (Gillberg, 1993; Wing, 1997). Evidence from neuroimaging and post-mortem studies suggests that ASD is accompanied by neuroanatomical differences in a variety of brain regions including the cerebellum (Courchesne et al., 1988), the amygdala–hippocampal complex (Aylward et al., 2002), fronto-temporal regions (Abell et al., 1999) and caudate nucleus (McAlonan et al., 2002). However, reported findings are highly variable and the neurobiology of ASD remains poorly understood.

Such high variability of findings among previous volume-based investigations might be explained in part by issues related to the high clinical heterogeneity of patients between studies. In addition, the investigation of distributed differences in brain anatomy, as expected in ASD, requires a spatially unbiased (e.g. mass-univariate) analytical approach, which is less likely to succeed due to conservative statistical thresholds. Mass-univariate approaches are suitable to the detection of large focal changes, but they have poor performance at dealing with small, distributed changes (Mourao-Miranda et al., 2005). Lastly, an increasing number of studies suggests that individuals with ASD have abnormalities in the development of several 'neural systems' (Ecker et al., 2012), and also display atypical functional connectivity (Assaf et al., 2010; Minshew and Williams, 2007; Poustka et al., 2011). Inter-regional correlations are, however, not generally utilized by conventional analysis mass-univariate techniques to examine neuroanatomical differences associated with ASD.

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The investigation between anatomical relationships among brain structures is referred to in literature as structural covariance (Mechelli et al., 2005). The neurophysiological meaning of structural covariance remains relatively unexplored. However anatomical features of interconnected regions are expected to be correlated (McAlonan et al., 2005; Mechelli et al., 2005) and have been explored between homotopic regions in contralateral hemisphere and gender differences. Using voxel-based-morphometry (VBM), Nosarti et al. (2011) reported structural covariance comparisons between preterm adolescents and full-term controls, identifying differences in several cortical and subcortical regions. Soriano-Mas et al. (2012) investigated gray-matter volumetric relationships of the neostriatum of healthy subjects. In children with ASD, McAlonan et al. (2005) characterized structural correlations between brain regions of the limbic-striatal 'social' brain systems in ASD.

Recently, pattern recognition methods based on machine-learning algorithms have been used to predict or classify individuals of different groups (Mourao-Miranda et al., 2005; Oliveira et al., 2010; Sato et al., 2008) on the basis of functional or structural magnetic resonance imaging (MRI) data (Fu et al., 2008; Kasparek et al., 2011; Plant et al., 2010). For instance, Ecker et al. (2010a,b) demonstrated that adults with ASD could be distinguished from neurotypicals on the basis of their neuroanatomy at a sensitivity and specificity of 90% and 80%, respectively. Similar accuracies have also been reported in children and adolescents with ASD (Uddin et al., 2011). Both of these studies were based on voxel-based values (gray/white matter probabilities) measured at each spatial location in the brain. However, to the best of our knowledge, nobody has yet applied pattern recognition algorithms to investigate the predictive value of covariance measures between morphometric features (e.g. cortical thickness) for symptom severity in ASD.

Notably, the use of pattern recognition methods to predict group membership (e.g.: patients vs. controls) or symptoms scales should not be viewed solely as a diagnostic/clinical tool. However, it can be used to develop objective biological measures for each individual from a set of sample data, which may provide insights into the neural substrates associated with a condition. Here we examined whether patterns of structural relationships between a set of brain regions are associated with autistic symptoms. This approach was based on the previous observation that Ecker et al. (2010a,b) predictive information on symptom severity is distributed across several brain regions or neural systems. We thus aim to evaluate whether the interaction between these regions also provides predictive value. Since autism is frequently associated with abnormalities in several neural systems/networks, it was expected that structural co-variations are of relevance to predict the presence of autistic symptoms.

In summary, the aims of the current study were: (i) to create a set of features representing inter-regional thickness correlations (IRTC) for each participant; (ii) to use these features within a machine-learning framework to evaluate whether structural covariance features are related to autistic symptoms in the ASD group; and (iii) to identify the most relevant regions in this structural analysis.

2. Material and methods

2.1. Participants

Eighty-two patients with ASD and eighty-four matched controls (all male, aged 18–42 years, mean age and full scale IQ ± standard deviation respectively: 26 ± 7 years and 110 ± 14; and 28 ± 6 years and 114 ± 12) were recruited by advertisement and examined at one of three centers: The Institute of Psychiatry, Kings College London; the Autism Research Centre, University of Cambridge; the Autism Research Group, University of Oxford. The patients were diagnosed following the ICD-10 research criteria and the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994). The Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1989) was used to evaluate the symptoms severity (mean ± s.d.: 9.26 ± 4.49 (3–21)), but it was not used as an inclusion criterion (scores of '3' for items were collapsed into '2'). All volunteers provided written informed consent, according to the approval from the National Research Ethics Committee, Suffolk, UK. The data from these patients have already been published in Ecker et al. (2012) in a voxel-based-morphometry study, where further details about this sample of patients can be found.

All participants with ASD were diagnosed according to ICD-10 research criteria, which were confirmed using the ADI-R to ensure that all ASD participants met the criteria for childhood autism. All cases reached ADI-R algorithm cut-offs in the three domains (language, social interaction, repetitive behaviors), although failure to reach cut-off in one of the domains by one point was permitted. Thus, although ADOS cut-off for autism is 10, the mean and range may be less as ADOS was not used as inclusion criteria. We used ADOS rather than ADI measures since the former may be more closely related to the current state of brain anatomy than past symptoms. Hence, it is not uncommon for individuals to meet ADI-R but not ADOS diagnostic criteria during adulthood. In the current study, we focused on the prediction of ADOS score because it has been used in the past to correlate measures of brain anatomy with current symptoms in many previous studies including our previously published AIMS papers (Ecker et al., 2010a, 2012).

2.2. MRI data acquisition

MRI data were acquired using 3T systems (8-channel RT head-coil) at three sites: Department of Radiology, University of Cambridge (GE Medical Systems HDx), Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings College London (GE Medical Systems HDx) and FMRIB Centre, University of Oxford (Siemens Medical Systems Trim Trio). A specialized and validated protocol (Deoni et al., 2008) was applied in order to guarantee standardization of acquisition in multiple sites studies.

For each subject, SPGR T1-weighted volumetric acquisition was performed with TR = 1800 ms, inversion-time = 850 ms, flip-angle = 20″, FOV = 25 cm, with 176 contiguous 1 mm^2 axial slices of 256 × 256 voxels with an in-plane resolution of 1 mm^2.

2.3. Image processing

The FreeSurfer analysis suite (http://surfer.nmr.mgh.harvard.edu/) was used to derive models of the cortical surface in each T1-weighted image. These well-validated and fully automated procedures have been extensively described elsewhere (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2004). In the present study, the pre-processed data considered at further analysis were the average cortical thickness measurements of each region from the cortex parcellation resulting in total of 70 parcellated regions (see Supplementary material).

2.4. Inter-regional thickness correlations

Fig. 1 presents the data flow of the approach proposed in the current study. Indexes for inter-regional thickness correlation (IRTC) are usually estimated using Pearson correlation between the cortical thicknesses of each region. If subsequent to normalizing the

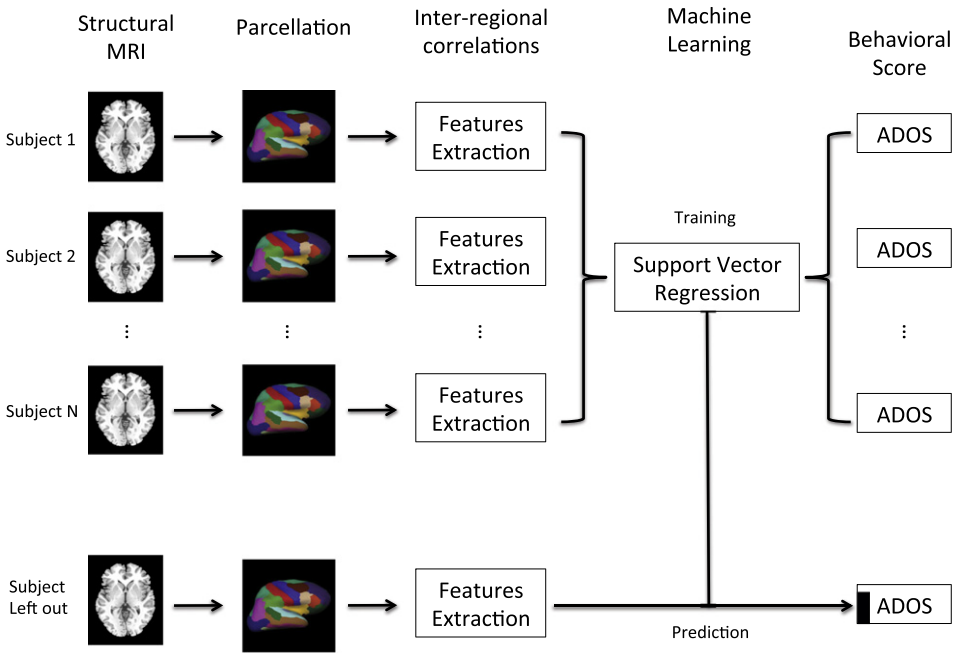

Fig. 1. Flowchart of preprocessing, support vector regression and leave-one-subject-out procedures.

thickness measures (subtracting the mean and dividing by the standard deviation), the correlation coefficient between two areas are calculated by:

$$r_{A,B} = \sum_{i=1}^{N} \frac{X_{A,i} X_{B,i}}{N},$$

where $X_{A,i}$ and $X_{B,i}$ are the normalized thickness measures in areas A and B of subject i, and N is the total number of subjects in the sample. IRTC can then be calculated for all pairwise combinations of M regions.

2.5. Features of IRTC for single subjects

An average of IRTC measure can then be calculated as the mean of all M pairwise correlations:

$$r_{mean} = \sum_{i=1}^{N} \sum_{j=1}^{M} \frac{X_{j,i} X_{j',i}}{NM} = \sum_{i=1}^{N} \frac{\sum_{j=1}^{M} \frac{X_{j,i} X_{j',i}}{M}}{N} = \sum_{i=1}^{N} \frac{c_i}{N},$$

where

$$c_i = \sum_{j=1}^{M} \frac{X_{j,i} X_{j',i}}{M}.$$

By using this measure, the average IRTC can be represented by the sum of single subject quantities. Thus, c_i can be viewed as the amount of mean IRTC from subject i, and it is the mean of all $(X_{j,i}, X_{j',i})$ pairs ($j = 1, 2, \ldots, M$). On the other hand, c_i is collapsing all information of pairwise correlations between regions in a single measure (the mean). We propose not only the mean (c_i) to be used as an individual feature of global (whole brain) dependence, but also the standard deviation of the pairs $(X_{j,i}, X_{j',i})$, as a variability descriptor. Briefly, given the thickness of parcellated regions from a single subject, these two measures (mean and standard deviation) were used as features depicting the inter-regional correlations for this subject.

In this study, healthy control data were solely used for normalization purposes (when subtracting the mean and dividing by the standard deviation of control group) as described previously in Section 2.4.

2.6. Use of IRTC to predict behavioral scores

By using the approach described in previous section, we used the two IRTC features of a subject as predictor variables to estimate ADOS, i.e., to evaluate the presence of current autistic symptoms. In order to build a non-linear prediction model, we applied the support vector regression with radial basis function (SVR) proposed by Smola and Schölkopf (1998), which is a well established approach for non-linear regression. In the current study, since the two explanatory variables were normalized to mean zero and variance one, the gamma parameter was set to 0.5 (i.e.: 1/[number of features]), which is a standard heuristic (Chang and Lin, 2001). In order to avoid overfitting problems, the ADOS predictions were carried out using the leave-one-out cross-validation technique.

In order to obtain a more detailed investigation of the dependence between IRTC and autistic symptoms, we also carried out separate analyses within hemispheres and a regional relevance. It is well known that some cognitive functions have an asymmetric laterality. In addition, we aimed to identify the most relevant regions for which IRTC contain more predictive information for ADOS scores. The cortical thickness correlations and support vector regression within hemispheres constituted a laterality analysis. The Spearman correlation coefficient between observed ADOS and the predicted score was calculated for the whole brain and within hemispheres to provide measure of accuracy. We considered Spearman correlation because it is more robust against outliers and violations of linearity when compared to Pearson correlation coefficients. The contribution (i.e. relevance) of each brain region was calculated using a leave-one-region-out approach. Similarly to the laterality analysis, Spearman correlation between observed and

predicted ADOS scores were calculated while leaving out one region at a time (instead one hemisphere). The differences between these correlations and the one when using the whole-brain IRTC provided a measure of contribution to the structural covariances for each brain region.

3. Results

Fig. 2 depicts the scatter-plot between leave-one-out predicted values and observed ADOS scores for individuals with ASD. For the whole-brain analysis, the correlation between predicted and observed scores was 0.362 ($p < 0.001$), indicating that measures IRTC can provide information about the severity of autistic symptoms. The left hemisphere analysis provided a correlation of 0.290 ($p < 0.001$). Interestingly, right hemisphere analysis resulted in a correlation coefficient of 0.072 ($p = 0.520$), suggesting a possible discrepancy between hemispheres in the dependence between IRTC and ADOS scores. Fig. 3 and Table 1 show the upper 10% of regions with most relevance in the prediction.

4. Discussion

In the present study, we introduced a novel approach to measuring inter-regional thickness correlations and to predict the presence of autistic symptoms measured by the ADOS. The left hemisphere was more relevant for the prediction of autistic symptoms than the right hemisphere. Speculatively, this laterality effect may be related either or both to the fact that all participants were male and right-handed. This suggests an influence of the language dominance, which is localized more frequently in the left hemisphere in males (Shaywitz et al., 1995) and/or an influence of the handedness (Pujol et al., 1999), which is represented by the contralateral (i.e. left) hemisphere.

Our proposed approach has important advantages when compared to conventional structural covariance analysis, as it is based on predictive information within individuals (e.g. individuals with ASD) and not – as traditionally – need covariances/correlations across a group of subjects. This property is of importance as it may be possibly explored as a potential objective biological marker for individuals rather than groups; i.e. the investigation of structural covariance at the group level is not suited to provide information about the accuracy on the level of individuals.

Brain abnormalities associated with ASD are complex and heterogeneous (Amaral et al., 2008; Toal et al., 2005), and the search for a neuroanatomical signature of ASD is thus inherently complicated. One reason for a lack of biomarkers for the condition is that ASD is associated with abnormalities in several large-scale neural systems (Minshew and Williams, 2007) rather than

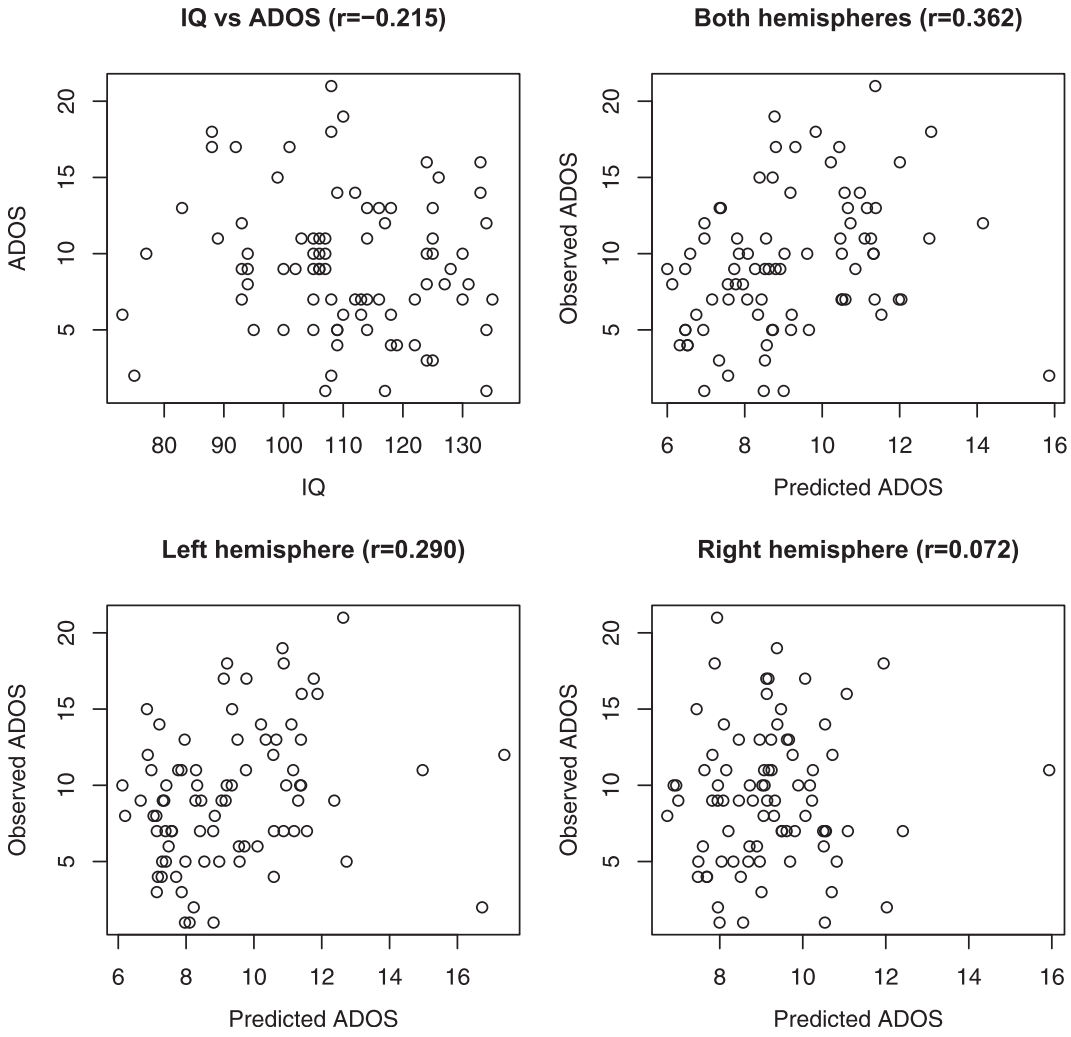

Fig. 2. Scatter-plot of leave-one-out predictions and observed ADOS based on the regions of whole brain, left and right hemisphere. The value of Spearman correlation coefficient between predicted and observed scores is shown in parenthesis.

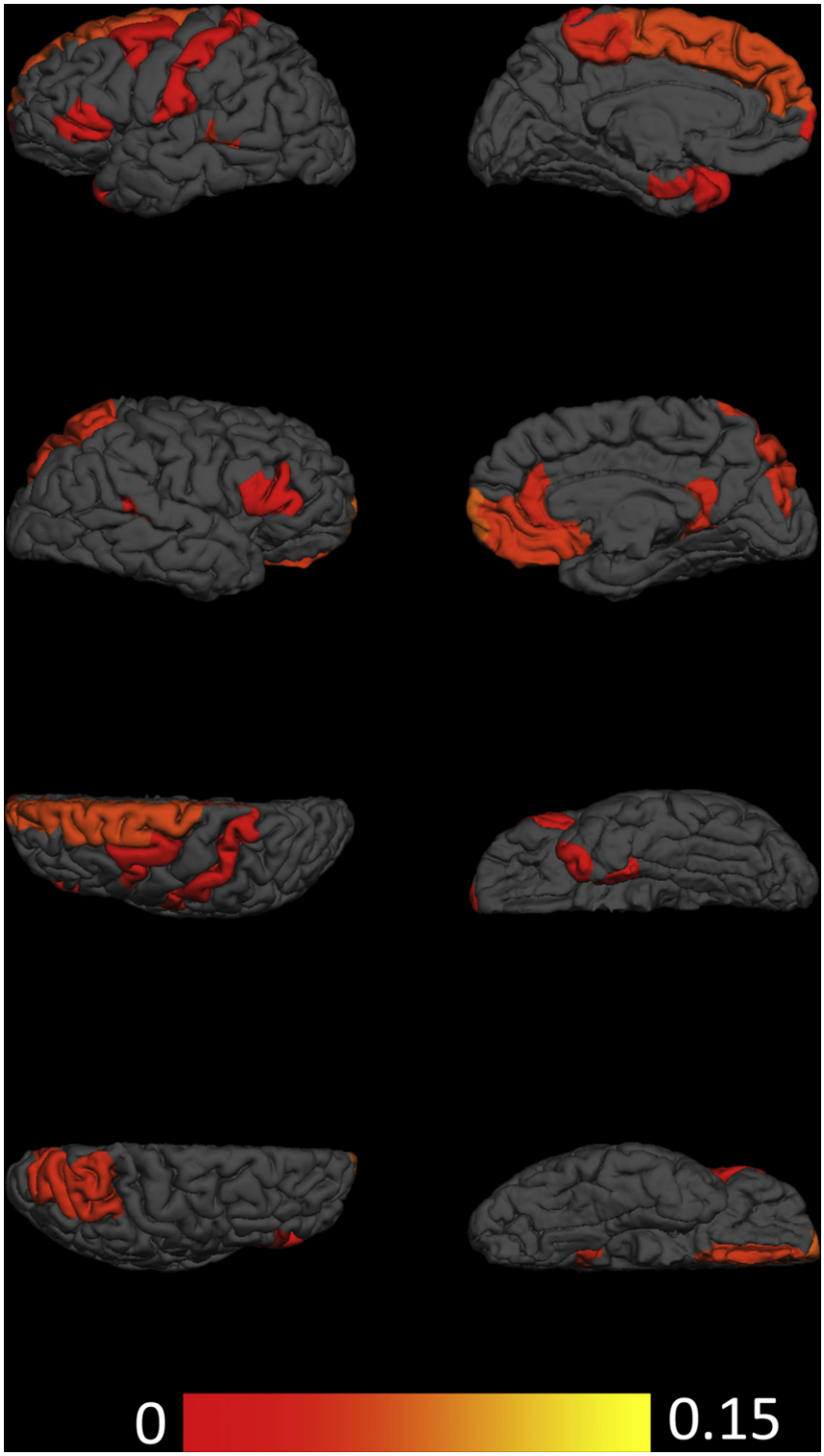

Fig. 3. Brain mapping of the 10% regions which IRTC were the most relevant to predict ADOS score. The color bar depicts the relevance value, which is measured by the decrement in correlation coefficient (between predicted and observed ADOS) when the region is excluded from IRTC calculation.

isolated brain regions. Here, we developed an approach, which allowed us to use information on the inter-regional correlational structure in order to make a prediction. Thus, instead of examining specific brain regions independently, our approach used mean measures of inter-regional correlations throughout the entire brain. This is a fundamental difference when compared to previous studies reported in literature (Ecker et al., 2010a,b) demonstrating that predictive information for autism diagnosis/severity is located in several spatially distributed patterns of neuroanatomical variation. In the present study, however, we explored whether the intercorrelations between components of this pattern might also be predictive for symptom severity.

Table 1
Regions with the most relevant IRTC for the prediction of ADOS scores. The relevance values are measured by the decrement in correlation coefficient (between predicted and observed ADOS) when the region is excluded from IRTC calculation.

Region	Relevance
Right pars triangularis	0.0526
Left post-central	0.0565
Left caudal middle frontal	0.0570
Left temporal pole	0.0585
Left pars triangularis	0.0589
Left frontal pole	0.0672
Left entorhinal	0.0678
Right banks of superior temporal sulcus	0.0710

Several structural and functional MRI studies have demonstrated that the degree of clinical impairments in individuals with ASD is associated with abnormalities in brain connectivity. For example, Assaf et al. (2010) found that the degree of functional connectivity between regions related to the default mode network was inversely correlated with ADOS scores in ASD. Also, abnormalities in white matter tracts that integrate fronto-temporal cortical networks were negatively correlated with symptom severity measured by the ADOS (Poustka et al., 2011). In this regard, our results complement previous data from functional and diffusion tensor imaging studies by showing that patterns of IRSC across the cortex may provide predictive value for the severity of autistic symptoms.

However, it is important to mention that the neurophysiological interpretation and mechanisms associated with inter-regional anatomical correlations remains speculation. Most previous investigations based on structural covariance note that activity-related morphological plasticity might lead to regional anatomical features (e.g.: cortical thickness, volume, shape, etc) correlations (McAlonan et al., 2005; Soriano-Mas et al., 2012). However, it is unclear whether these correlations result from shared developmental influences (i.e. neurotrophic factors) or may be related to common experience-related plasticity (Mechelli et al., 2005). This alternative hypothesis is supported by the observation that the volume of some regions of the visual system (such as the lateral geniculate nucleus, the primary visual cortex, etc.) is significantly correlated across individuals (Andrews et al., 1997). Furthermore, specific brain regions undergo a common age-related decline in volume (Raz et al., 1997). In this sense, our findings could be explained not only by plasticity induced inter-regional interactions, but also by shared environmental influences. Alternatively, as autism is associated with both abnormalities in neural systems (circuits) which, in turn, may be linked to environmental factors, it remains unknown whether nature or nurture induces shared neuroanatomical variation.

The present study has some methodological limitations. Due to the relatively small sample size, it was not possible to explore whether global inter-regional correlations of cortical thickness may reliably predict symptoms' severity of different subgroups of autism (e.g. individuals with Asperger's syndrome). Secondly, total ADOS scores may be confounded by coping strategies developed across the life-span and may therefore not accurately represent the severity of current autistic symptoms on a global scale. Also, it has been noted that ADOS scores do not provide 'standardized' measures of symptom severity and hence scores may not be comparable across modules and/or subject groups. Here, we specifically administered module 4 in all of our adult cases, which is why our results cannot fully be explained by this limitation. Moreover, we have recently demonstrated that ASD classifiers based on the brain anatomy are more closely related to current symptoms (i.e. ADOS scores) than past symptoms (i.e. ADI-R scores) (Ecker et al., 2010a). Hence, our results add to the emerging evidence that the current state of the brain (e.g. in adulthood) is more closely related to current autistic symptoms than past symptoms in childhood. In addition, future research is needed to investigate the clinical specificity of the proposed classifier, as we did not include data of an alternative clinical population (e.g. individuals with ADHD).

Conflict of interest

João Ricardo Sato, Marcelo Queiroz Hoexter, Pedro Paulo de Magalhães Oliveira Junior, Michael John Brammer, MRC AIMS Consortium, Declan GM Murphy and Christine Ecker have declared no conflict of interest.

Contributors

CE, DM and MRC Consortium designed the study and wrote the protocol. MRC Consortium collected the data. JRS, MQO, MJB, PPO and CE wrote the manuscript. JRS and MJB undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jpsychires.2012.11.017.

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