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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