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Autism is associated with inter-individual variations of gray and white matter morphology

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**Short title:** Autism-related integration of gray and white matter

**Key words:** autism, multimodal analysis, multivariate analysis, gray matter, white matter, canonical correlation analysis
Abstract

Background

Although many studies have explored atypicalities in gray and white matter (GM, WM) morphology of autism, most of them rely on unimodal analyses that do not benefit from the likelihood that different imaging modalities may reflect common neurobiology. We aimed to establish brain patterns of modalities that differentiate between autism and controls and explore associations between these brain patterns and clinical measures.

Methods

We studied 183 individuals with autism and 157 non-autistic individuals (6-30 years) in a large deeply phenotyped autism dataset (EU-AIMS LEAP). Linked Independent Component Analysis was utilized to link all participants’ GM volume and WM diffusion tensor images, and group comparisons of modality shared variances were examined. Subsequently, we performed univariate and multivariate brain-behavior correlation analyses to separately explore the relations between brain patterns and clinical profiles.

Results

One multimodal pattern was significantly related to autism. This pattern was primarily associated with GM volume in bilateral insula, frontal, pre- and post-central, cingulate, and caudate areas, and co-occurred with altered WM features in the superior longitudinal fasciculus. The brain-behavior correlation analyses showed a significant multivariate association primarily between brain patterns that involved variation of WM, and symptoms of restricted and repetitive behavior in the autism group.

Conclusions

Our findings demonstrate the assets of integrated analyses of GM and WM alterations to study the brain mechanisms that underpin autism, and show that the complex clinical autism phenotype can be interpreted by brain covariation patterns that are spread across the brain involving both cortical and subcortical areas.
Introduction

Autism Spectrum Disorder (autism) is a heterogeneous condition characterized by difficulties with social and communicative behaviors, repetitive, rigid behaviors and altered sensory processes (1). In search of the brain basis of autism, the condition has been associated with multiple morphological differences in gray matter (GM) and white matter (WM) (2, 3), as reported by magnetic resonance imaging (MRI) studies. However, former studies have shown heterogeneous findings of the alterations in both cortical (e.g., cortical thickness, surface area, volume) and subcortical (e.g., volume) morphometry in multiple brain regions making it difficult to define the neural correlates of autism (3-5). Additionally, voxel-wise GM volume analyses revealed divergent results, for instance, in temporal areas in autism (6-8). Studies of WM microstructural associations in autism are similarly heterogeneous in their findings (2, 9, 10). One explanation for discrepant and heterogeneous findings is that the studies differ widely in data analytic strategy - i.e., these studies rely on unimodal analyses techniques that ignores the signal of interest probably present in more than one modality (11). Additionally, when integrated together these modalities might provide additional analytical sensitivity.

This prompted research to move beyond unimodality and incorporate and connect data from different imaging modalities. For example, (12) suggested that GM variation in autism is generally accompanied by WM variation; (13) showing higher axial diffusivity (L1) in the WM fiber tracts originating and/or terminating in the GM clusters with increased local gyrification in adults with autism. Despite the progress away from unimodal approaches, in essence, these MRI studies which correlate GM and WM measures do so after separate unimodal statistical analyses. This likely has less sensitivity to assess the biological variance than fully integrating multimodal data analysis across participants.

It is assumed that a relatively high level of co-occurring neurobiology underlying different aspects of brain morphology due to the complicated natures of autism. Therefore, efficient modeling of this potential shared variance would increase the chances to produce a more
complete picture of autism in a specific perspective (i.e., brain morphology in our study). Here, we aim to utilize an integrative multimodal approach, linked independent component analysis (LICA), to simultaneously incorporate several imaging modalities allowing the investigation of inter-subject variability across modalities in one analysis (14, 15), which equips the ability to isolate the artifacts and may increase the sensitivity to correlate the remaining signals with variables of interest (14). So far, studies that highlight the underlying shared variance between modalities using LICA in autism remain scarce. Previous studies revealed case-control differences between adults with autism and typically developing individuals in linked patterns of voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) measures in several brain regions (16, 17). However, these studies focused exclusively on adult autistic individuals without intellectual disability and were comprised of relatively small sample sizes (<100 individuals) (16, 17). Autism is a highly diverse condition; we therefore investigate brain patterns in a broader more representative autism sample which might help better characterize brain patterns of autism - one of the aims of the current study. We hypothesized that the model analysis would reveal the autism-related regional correspondence between GM and WM or modality-specific effect.

In addition to identifying categorical group differences, dimensional analyses, i.e., analyses of continuous scores of autism symptoms might capture more of the heterogeneity of autism compared to categorical diagnostic labels. Many studies have demonstrated the univariate connections between GM or WM patterns and the core symptoms of autism (e.g., (2, 3)). Nonetheless, the relationships between brain substrates and clinical phenotypes are potentially the outcome of integrative effects across multiple autism symptom domains and brain areas, and therefore the multidimensional associations between brain covariations and core symptoms of autism need to be clarified. We therefore performed univariate analyses to identify the one-to-one dimensional associations and additionally implemented a multivariate analysis using canonical correlation analysis (CCA) to learn the integrated associations (18).
Similarly, we furthermore expected CCA would help to elucidate the potential correlation between brain and behavior.

This study was designed to overcome the aforementioned limitations of previous work by applying LICA to the Longitudinal European Autism Project (LEAP) dataset (19) to link the sources of variance of voxel-wise GM volume and WM diffusion tensor measures. The LEAP dataset provides a deeply phenotyped and comprehensively biologically assessed multisite sample of individuals with/without autism that allows relating the results of LICA to clinical characteristics of the participants. More specifically, we applied (a) a univariate approach to identify categorical group difference of linking brain patterns, and subsequently their one-to-one relations to continuous measures of autism symptoms; (b) a multivariate method (i.e., CCA) to further quantify the association between two datasets of brain patterns and autistic traits in the autism group.
Methods and Materials

Participants

The participants were part of the EU-AIMS and AIMS-2-TRIALS Longitudinal European Autism Project (LEAP) dataset - a large multicenter study aimed at identifying and validating biomarkers in autism (19, 20). Individuals with autism were included based on an existing clinical diagnosis according to DSM-IV, DSM-IV-TR, DSM-5, or ICD-10. Each participant underwent clinical, cognitive, and MRI assessment at one of six collaborative centers. We refer to (19, 20) for further details on experimental design and clinical characterization. In the present study, diffusion-weighted image (DWI) data at timepoint 1 were only available from participants in three centers. Therefore, the participants were selected who had both T1-weighted and DWI data available from the following centers: Institute of Psychiatry, Psychology and Neuroscience, King’s College London, United Kingdom; Radboud University Medical Centre, Nijmegen, the Netherlands; Central Institute of Mental Health, Mannheim, Germany (Supplementary Section 1).

The final sample comprised 344 participants between 6 and 30 years, including 185 autistic individuals (133 male and 52 female, IQ≥40), and 159 non-autistic individuals (99 male and 60 female, IQ≥50). The demographic and clinical information of the final sample is summarized in Table 1. For the details on exclusion criteria, please see Supplementary Section 2.

Clinical measures

The Autism Diagnostic Interview-Revised (ADI) (21) and the Autism Diagnostic Observational Schedule 2 (ADOS) (22) were used to measure the past (ever and previous 4-to-5 years) and current core symptom severities of autism from social interaction, communication, and restricted repetitive behaviors (RRB) domains. Specifically, the calibrated severity scores (CSS) for subscales and total of ADOS were calculated to use in the following analyses (23, 24). Additionally, we used several parent-reported scales to assess autism
symptoms, including the Social Responsiveness Scale 2nd Edition (SRS) (25) capturing the
social-communication variations, the Repetitive Behavior Scale-Revised (RBS) (26) identifying
the repetitive and rigid behaviors, and the Short Sensory Profile (SSP) (27) evaluating the
sensory processing variations. Concerning the potential effect of Attention Deficit
Hyperactivity Disorder (ADHD), anxiety and depression co-occurrence, we separately included
the scores from the ADHD DSM-5 rating scale (28), anxiety and depression from the
Development and Well-Being Assessment (DAWBA) (29) as additional covariates in the post-
hoc analyses. There was a substantial amount of missing clinical data, which could greatly
reduce the power of our analysis. To tackle the missing clinical data and fully harness the large
LEAP sample size we used imputed clinical data (30). The imputation procedure developed by
our colleagues considering the potential non-randomness of missing data, who developed
quantitative measures to assess the quality of the imputations, and finally imputed data
adopting a non-parametric tree regression model embedded in an iterative round Robin
iterative schedule (30). The details of missingness of the current sample can be found in
Supplementary Section 3.

**MRI data acquisition**

All participants were scanned on 3T MRI scanners. High-resolution structural T1-weighted
images were acquired using magnetization-prepared rapid gradient-echo sequence with full
head coverage, at 1.2 mm thickness with 1.1×1.1 mm in-plane resolution. Diffusion-weighted
imaging (DWI) scans were acquired using echo-planar imaging sequence, at 2 mm thickness
with 2.0x2.0 mm in-plane resolution.

MRI data acquisition parameters can be found in the Supplementary Section 4.

**Image processing**

**GM volume estimation**

Structural T1 images were preprocessed according to CAT12 toolbox (https://dbm.neuro.uni-jena.de/cat/) pipeline in SPM12 (Wellcome Department of Imaging
Neuroscience, London, UK) to obtain VBM data, which is a spatially-unbiased whole-brain approach extracting voxel-wise GM volume estimations. T1-weighted images were automatically segmented into GM, WM, and cerebrospinal fluid and affine registered to the MNI template. A high-dimensional, nonlinear diffeomorphic registration algorithm (DARTEL) (31) was used to generate a study-specific template from GM and WM tissue segments of all participants, and then to normalize all segmented GM maps to MNI space with 2mm isotropic resolution. All GM images were smoothed with a 4mm full-width half-max (FWHM) isotropic Gaussian kernel.

**Diffusion parameters**

DWI images from all sites were preprocessed using the same pipeline. De-noising was performed using the Marchenko-Pastur principal component analysis (MP-PCA) method (32). Subsequently, Gibbs-ringing artifacts were removed according to (33). FSL *eddy* was employed to correct the eddy-current induced distortions and subject motion (34). To improve the final quality of data and recover most of the motion artifacts, we utilized intra-volume slice motion correction (35). Quality control reports were then generated for each subject and each site (36).

Individual voxel-wise FA, mean diffusivity (MD), mode of anisotropy (MO), L1 and radial diffusivity (RA) maps were derived using *dtifit* in FSL (37). These five DTI features were selected on account of the different aspects of white matter microstructure, for example, FA measures the degree of anisotropic movement of water molecules and L1 represents the magnitude of the diffusion in the primary direction, which are related to myelin structure or myelination. FA images were processed using Tract-Based Spatial Statistics (TBSS) pipeline including registration of all images to FMRIB58_FA standard space, skeletonization of the mean group white matter and projection of each individual’s data onto the skeleton (38). The mean skeleton image was thresholded at FA 0.2. Other DTI measures (MD, MO, L1, RA) were projected onto the FA skeleton using the *tbss_non_FA* option. All DTI data had 1mm isotropic
resolution when entering the following data fusion model.

A full quality control report and additional preprocessing details of the GM and WM images are included in the Supplementary Section 2.

Modalities fusing analysis

The shared inter-participant variations across six features (i.e., VBM, FA, MD, MO, L1, RA) were explored using LICA (11). LICA is able to factorize the multiple input modalities simultaneously into modality-wise independent components (ICs) while importantly constraining all decompositions to be linked through a shared participant-loading matrix, which describes the amount of contribution of each participant to a specific IC. In addition to the participant-loading matrix, this method provides, per IC, a vector reflecting the contribution (weight) of each modality and a spatial map per modality showing the extent of the spatial variation. All mathematical algorithms of LICA are detailed in (11). As the model order is recommended to be less than 25% of the sample size (11, 14), 80-dimensional factorization was chosen to perform LICA. A multimodal index (MMI) (39) (Supplementary Information Section 5) was calculated to present the contribution uniformity of the modalities in each IC. This results in a scalar value where 0 would equate to 100% unimodal contribution and 1 would mean equal contributions from all modalities.

Statistical approach

The participant-loadings characterize the inter-individual variations of the uni/multimodal effects, and in the current study, they were used for the analyses of group differences between autistic and non-autistic individuals, and for associations with behavioral measures. Results reported in the main text are performed using imputed data to maximize the statistical power. All analyses were replicated using the original non-imputed data.

Case-control difference

A generalized linear model (GLM) was utilized to examine group differences of the brain’s inter-participant variations in LICA outputs while controlling for age, sex, IQ, and scanner site.
Multiple comparison (number of tests=80) correction was implemented using false discovery rate (FDR) (p<0.05) (40). In addition to considering the effects of co-occurring conditions on case-control difference, we separately investigated the age-by-group, IQ-by-group, sex-by-group and site-by-group interactions, and medication use effects on brain pattern(s) with the case-control difference.

**Brain-behavior associations**

Similarly, we used a GLM to explore the univariate associations between each IC and subscales of ADI and ADOS, SRS, RBS, and SSP in the autism group while controlling for age, sex, IQ and scanner site. We corrected for multiple comparisons (number of tests = 80 x number of (sub)scale(s)) with FDR (p<0.05).

Subsequently, we utilized one CCA (18) to better picture the overall association between all brain ICs and subscales of ADI and ADOS, and total scores of SRS, RBS, and SSP in the autism group. CCA is a multivariate approach to simultaneously learn two sets of linear projections corresponding to the brain ICs and the behavioral profiles, which maximizes the correlation between two sets of variables at the participant level. In such maximized correlation, the evaluation of brain-behavior relationships is on the basis of the respective contribution of each IC and each behavioral profile to the correlation, which can be measured by the loading of each variable (transformed from canonical coefficient) described previously (41). Additionally, the canonical variates are calculated respectively for the brain and the behavioral sets according to the product of the canonical coefficients and the original sets. In this study, we referred to each pair of canonical variates as CCA mode. Before entering the CCA model, age, sex, IQ and scanning site were controlled for both brain and behavior profile datasets using Huh-Jhun residualization method (42, 43). The statistical significance of CCA modes was assessed by a complete permutation inference algorithm proposed by (43), where both brain and behavior data were permuted separately across all participants with 10,000 iterations. For each CCA mode’s multiple testing correction, we used stepwise cumulative maximum
approach, p<0.05, see details in (43). We further tested the reliability of the CCA findings and the stability of each loading of the significant CCA mode(s) using a leave-one-subject-out approach.
Results

Group effect of brain components

We obtained 80 ICs from the multimodal integration analysis in our study. The modality contributions (for 80 ICs) and MMI of each IC can be found in Supplementary Section 5. We subsequently used the participant-loadings of the 80 ICs to test for group differences and found one component (IC58) with a significant case-control difference (β=-0.192, t(337)=-3.595, FDR corrected p=0.030; Figure 1). The respective contributions of the modalities in IC58 are 26.0% from VBM, 18.4% from FA, 17.9% from MO, 13.8% from L1, 13.7% from RA, and 10.2% from MD, indicating that various MRI features share variance associated with autism. In Figure 1, we present the summarized images of each modality’s spatial map of IC58. The spatial patterns show autism-related smaller GM volume in the bilateral insula, inferior frontal gyrus (IFG), orbitofrontal cortex (OFC), precentral, postcentral gyrus, lateral occipital cortex (LOC), inferior temporal gyrus (ITG), angular gyrus (AG), posterior division of cingulate gyrus (PCC), and precuneus cortex, and larger GM volume in calcarine cortex, bilateral middle frontal gyrus (MFG), caudate and anterior division of cingulate gyrus (ACC). Correspondingly, autism-related DTI features were found in bilateral superior longitudinal fasciculus (SLF), corticospinal tract (CST), and inferior fronto-occipital fasciculus (IFOF). In addition to these fasciculi, RA and MD in the cingulum and anterior thalamic radiation were also implicated. Taken together, the implication of SLF and their adjacent GM volumes; frontal, precentral, and postcentral areas (Supplementary Section 6) in autism indicate that variations of GM volumes and WM microstructure are linked in these brain locations, rather than modality or tissue dependent.

Post-hoc, to assess the respective influences of co-occurring conditions, interactions of diagnosis-by-age, -sex or -IQ, and medication use on the multimodal IC found significantly associated with group, we additionally included them as separate covariates in the GLM of IC58. The analysis showed that the group effect of IC58 was robust to the inclusion of these additional covariates in the model (p<0.01). However, we found a significant moderate site-
by-diagnostic group interaction effect on the current result ($G^2(2)=6.860$, $p=0.032$). This was driven by having significant effects in 2 of the 3 sites with no significant differences at the third. Details are in Supplementary Section 7.

**Relating brain patterns to behavior profiles**

We conducted the univariate (GLM) and multivariate (CCA) correlation analyses on brain and behavior data in the autism group only. No significant univariate brain-behavior relationship in the autism group was found (FDR corrected $p>0.120$). We did however find a significant multivariate association pattern of CCA ($r=0.823$, corrected $p=0.006$, Figure 2). The proportion of total variance explained by this multivariate pattern was 20.8% for brain ICs and 14.2% for behaviors. In this multivariate associated pattern, multimodal IC7 (canonical loading: -0.334) and IC78 (canonical loading: 0.283) showed the strong contributions to the correlation with autism core symptoms, and from a phenotypic perspective this multivariate pattern demonstrated a strong association with the ADI RRB and ADOS RRB subscales. WM microstructure mainly dominated in IC7 and IC78. IC7 mainly included right inferior longitudinal fasciculus (ILF), IFOF, and CST, and IC78 primarily involved bilateral anterior thalamic radiation and SLF. These two predominant ICs highlight the involvement of WM in autism symptoms. The loadings of each brain component of this CCA mode can be found in the Supplementary Section 8. The leave-one-subject-out analysis indicated that the significant CCA mode of CCA analysis was reliably estimated (Supplementary Section 9). We additionally ran a CCA model excluding SSP to probe the effect the imputed SSP scores (42%) specifically may be having and found the entire structure of the output did not differ greatly (Supplementary Section 10).

The results using non-imputed data of group effect and univariate brain-behavior association were similar to the main results. The different CCA patterns using non-imputed data were reasonable owing to the large amount of missingness (Supplementary Section 3).
Discussion

We examined autism-related inter-individual variance of integrated GM-WM morphology in a large European sample of individuals with and without autism across a broad age and IQ range. Analyses showed a significant diagnostic-group effect of the linked GM-WM pattern that supports our hypothesis of the link between GM and WM morphology alterations in autistic individuals. In particular, the GM volume variation in pre- and post-central areas converged with the WM microstructural variation in the SLF. This spotlights the shared variances between GM and WM morphology in these brain areas in autism, and suggests the structural associations in autism are not only limited to localized regions but also involve the WM pathways connecting these brain areas. In a next set of analyses, we found a significant integrative association between brain patterns and autism core symptoms using CCA in the autism group, where the identified brain multimodal patterns underline the important role of WM morphology.

Notably, the autism-specific VBM pattern on this multimodal analysis replicates our previous unimodal GM volume covariation study in a larger overlapped sample of the EU-AIMS project to a certain extent (8). The areas of bilateral insula, IFG, OFC, and caudate form a steady autism-related covariation pattern in previous and current studies. These areas were demonstrated previously to relate to repetitive behaviors and reward-based decision-making abilities in autism (44, 45). The covariation of insula and frontal areas in our studies indicates the consistency and stability of the co-occurring GM morphological alterations in autism. Benefitting from multimodal/multivariate approaches suggested by previous studies (46, 47), the application of the LICA approach modeling the shared variances across modalities, extends identified autism-related GM associations to pre-central, post-central, occipital and temporal areas and additionally links with significant WM findings of DTI measures.

Our results indicated one covarying set of brain GM and WM areas associated with autism diagnosis. In this multimodal set, GM volume in cortical and subcortical regions and
microstructure in WM tracts (mainly SLF, CST and IFOF) were implicated and these regions/tracts have previously been identified in unimodal analyses (10, 44, 48-50). This broad range of brain regions along with large WM bundles associated with autism is in accord with the notion that the neural correlates of autism are widespread in brain regions and connectivity patterns (51-53). This also corresponds with another multimodal autism study reporting extensive autism-related brain areas (16). The areas of this IC have been linked previously to both social and non-social cognitive difficulties in individuals with autism, varying from visual, sensory and motor processing to high-order cognitive abilities (10, 54-57). For example, pre-central, post-central gyrus, SLF and CST are related to (sensory-)motor processing and have been implicated in autism (10, 50, 58). These adjacent affected areas (grouped areas of pre-, post-central areas and SLF, CST; grouped areas of LOC and IFOF occipital section) in our findings logically is in line with the brain organization principles during development, which states that nearby areas tend to be more interconnected (59, 60). In summary, the autism diagnosis-related co-varying GM-WM pattern reflect that autism is a complex condition associated with neural morphology. However, we did not find any significant univariate relationship between behavioral phenotypes and brain patterns. This is probably a result of the diverse phenotypes in our sample (i.e., complex and heterogenous nature of autism), therefore, the compound variances of the symptom profiles cannot be explained by single uni/multimodal brain patterns. Additionally, imaging studies suggested that individuals with autism develop alternative processing strategies (52) that might mix or neutralize the manifestations of behavioral phenotypes in autism moderating detection of well-established brain-behavior relations. Furthermore, non-significant univariate but one remarkable multivariate brain-behavior relationship in current study may relate to the relatively mild autism traits in LEAP cohort, for example, the average score of ADOS CSS total is lower than the clinical cutoffs, which was reported in the larger LEAP sample compared to other cohorts (20).
The significant multivariate brain-behavior relationship in the current study is one prominent WM dominated multivariate relation between all brain patterns and all behavioral profiles. The top two ranking ICs emphasize the importance of WM connection to the core traits of autism. Multivariate/multimodal analysis increases the difficulty in interpreting findings, as it's challenging to clarify the direction of each association. Nonetheless, coinciding with previous studies (2, 10, 50, 61, 62), there are associations of ILF, IFOF, CST, SLF and SLF microstructural measures with core symptoms/traits in autism. In line with previous findings our work also shows laterality effects with much of the contribution from IC7 being right lateralized in autism (55, 63). Significantly, GM volume contributed only by a small amount, which implicates WM morphology has a stronger connection to the autism behavioral phenotypes compared to GM in this multivariate correlation. In our previous GM work a multivariate correlation pattern exhibited a strong association between RRB scores of ADI and ADOS and GM covariations in autism, while here when including WM microstructural measures, the brain patterns demonstrated a strong association with RRB domains of the ADI and ADOS. This multivariate brain-behavior association needs further investigation to determine the relationship between the development of WM microstructure and behaviors, the generalizability beyond the current sample, and to explore how different behavioral scales capture behavioral phenotypes in autism, which might expand our knowledge of current brain-behavior association patterns.

Our findings should be interpreted with regard to several limitations. First, to generalize our pattern of brain alterations associated with autism requires replication in other large-scale datasets. Second, the current multimodal dataset included fewer participants than our previous work (8), which may have lowered statistical power when detecting the group effects and brain-behavior associations in autism group. Despite that, this is still the largest multimodal MRI study of autism to date and includes a diverse sample of autistic and non-autistic participants. Third, limited to the cross-sectional nature of the current study, our
findings are deficient to address the developmental effects on these brain patterns and their relations to the behavior profiles, as the structures of the brain (especially WM) change remarkably over puberty and with aging.

In current study, we demonstrate autism-related inter-individual covariations of GM volume in frontal, pre-central, post-central and occipital areas and microstructure in associated WM fasciculi. Together, these GM and WM alterations are part of the underlying neural substrates of the phenotypes in autism. Subsequently, we highlight the potential role of WM, in the relation to the core symptoms of autism. Further studies may link our GM-WM morphometric findings with brain function acquired from cognitive assessments and/or functional MRI data.
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Disclosures

TC has received consultancy from Roche and Servier and received book royalties from Guildford Press and Sage. DGM has been a consultant to, and advisory board member, for Roche and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. CFB is director and shareholder in SBGNeuro Ltd. TB served in an advisory or consultancy role for ADHS digital, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker’s fee by Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press. JKB has been a consultant to, advisory board member of, and a speaker for Janssen Cilag BV, Eli Lilly, Shire, Lundbeck, Roche, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents or royalties. The present work is unrelated to the above grants and relationships. The other authors report no biomedical financial interests or potential conflicts of interest.
References

2006;31(4):1487-505.
Table 1. Demographic information of participants\(^a\)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Autism, n=185</th>
<th>Controls, n=159</th>
<th>(t/\chi^2)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age, years(^b)</td>
<td>17.30 5.22</td>
<td>17.51 5.19</td>
<td>0.369</td>
<td>0.712</td>
</tr>
<tr>
<td>IQ(^b),(^c)</td>
<td>98.90 20.44</td>
<td>102.68 19.10</td>
<td>1.769</td>
<td>0.079</td>
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<tr>
<td>n=154</td>
<td>n=142</td>
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<tr>
<td>IQ(\geq75)</td>
<td>105.47 15.30</td>
<td>107.32 14.04</td>
<td>1.083</td>
<td>0.028</td>
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<td>n=31</td>
<td>n=17</td>
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<tr>
<td>IQ&lt;75</td>
<td>66.28 6.95</td>
<td>63.88 8.55</td>
<td>-0.994</td>
<td>0.329</td>
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<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Sex, male/female(^d)</td>
<td>133/52 71.9/28.1</td>
<td>99/60 62.3/37.7</td>
<td>3.610</td>
<td>0.057</td>
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**Symptom Profiles**

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<tr>
<th>ADI</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>Social Interaction</td>
<td>16.54</td>
<td>6.95</td>
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<tr>
<td>Communication</td>
<td>13.35</td>
<td>5.57</td>
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<tr>
<td>RRB</td>
<td>4.07</td>
<td>2.58</td>
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<table>
<thead>
<tr>
<th>ADOS CSS</th>
<th>Mean</th>
<th>SD</th>
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<tr>
<td>Total</td>
<td>5.40</td>
<td>2.75</td>
</tr>
<tr>
<td>Social Affect</td>
<td>6.06</td>
<td>2.64</td>
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<tr>
<td>RRB</td>
<td>4.70</td>
<td>2.77</td>
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</table>

<table>
<thead>
<tr>
<th>SRS raw score(^e)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.80</td>
<td>11.55</td>
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</table>

<table>
<thead>
<tr>
<th>RBS(^f)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.54</td>
<td>13.54</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>SSP(^e)</th>
<th>Mean</th>
<th>SD</th>
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</thead>
<tbody>
<tr>
<td>142.16</td>
<td>23.63</td>
<td></td>
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</table>

\(^a\) IQ and symptoms profiles reported are the imputed data (30).

\(^b\) Statistical differences were assessed by two-sample t-test. Degrees of freedom of the two t-tests were 342.

\(^c\) IQ ranged from 40 to 148 in the ASD group and from 50 to 142 in the control group.

\(^d\) The differences were examined by the chi-square test.
In SRS, RBS and SSP questionnaires, we used parent-rated report.

SD, standard deviation; IQ, full-scale intelligence quotient; ADHD, Attention Deficit Hyperactivity Disorder; ADI, Autism Diagnostic Interview-Revised; RRB, restricted, repetitive behaviors; ADOS, Autism Diagnostic Observational Schedule 2; CSS, calibrated severity scores; SRS, Social Responsiveness Scale 2nd Edition; RBS, Repetitive Behavior Scale-Revised; SSP, Short Sensory Profile.
Captions

**Figure 1** The multimodal component shows significant case-control difference. The relative contribution of each feature is displayed in brackets. The VBM spatial map is thresholded at $5<|Z|<10$. Clusters of DTI features were filled and thresholded at $3<|Z|<10$, then smoothed using a 0.3mm Gaussian kernel in FSL for visualization purposes. VBM, voxel-based morphometry; FA, fractional anisotropy; MO, mode of anisotropy; L1, axial diffusivity; RA, radial diffusivity; MD, mean diffusivity.

**Figure 2** The multivariate association pattern (i.e., CCA mode) was found significant between the two sets of brain components and all behavioral profiles. A displays the scatterplot of this correlation (between the CCA mode), and x, y axes are the pair of CCA variates. One dot in each participant is coded with gradient color regarding to the RRB subscale of ADI. B demonstrates the loading of each behavioral (sub)scale in this CCA mode. C shows the modality contributions to the components displayed in D. D exhibits the two multimodal components with the strong contribution to the correlation with autism core symptoms, where the top two loading modalities in each component are shown in the figure. The canonical loading of each component is shown in the brackets. The modality spatial maps are thresholded at $3<|Z|<10$. The CCA was only performed in autism group. CCA, canonical correlation analysis; ADI, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observational Schedule 2; SA, social affect; RRB, restricted repetitive behavior; IC, independent component; MO, mode of anisotropy; RA, radial diffusivity; MD, mean diffusivity; FA, fractional anisotropy; L1, axial diffusivity; VBM, voxel-based morphometry.
Figure A: CCA variates: behavioral scales
- x = 0.823
- ADI RRB score
  One dot per participant

Figure B: CCA variates: participant loadings of brain ICs

Figure C: The loadings of behavior variables of the CCA mode
- IC7
- IC78

Figure D: IC7 (loading: -0.334)
- MD (44.0%)
- L1 (29.5%)
- IC78 (loading: 0.283)
- MD (22.9%)
- RA (21.4%)

Modality contributions of the two high loading components