The Autism Brain Imaging Data Exchange: Towards Large-Scale Evaluation of the Intrinsic Brain Architecture in Autism

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Conflict of Interest

Catherine Lord receives royalties from the publication of the Autism Diagnostic Interview—Revised and the Autism Diagnostic Observation Schedule. All other authors declare no conflict of interest.
Abstract

Autism spectrum disorders (ASD) represent a formidable challenge for psychiatry and neuroscience because of their high prevalence, life-long nature, complexity and substantial heterogeneity. Facing these obstacles requires large-scale multidisciplinary efforts. While the field of genetics has pioneered data sharing for these reasons, neuroimaging had not kept pace. In response, we introduce the Autism Brain Imaging Data Exchange (ABIDE) – a grassroots consortium aggregating and openly sharing 1112 existing resting-state functional magnetic resonance imaging (R-fMRI) datasets with corresponding structural MRI and phenotypic information from 539 individuals with ASD and 573 age-matched typical controls (TC; 7–64 years) (http://fcon_1000.projects.nitrc.org/indi/abide/). Here, we present this resource and demonstrate its suitability for advancing knowledge of ASD neurobiology based on analyses of 360 males with ASD and 403 male age-matched TC. We focused on whole-brain intrinsic functional connectivity and also survey a range of voxel-wise measures of intrinsic functional brain architecture. Whole-brain analyses reconciled seemingly disparate themes of both hypo and hyperconnectivity in the ASD literature; both were detected, though hypoconnectivity dominated, particularly for cortico-cortical and interhemispheric functional connectivity. Exploratory analyses using an array of regional metrics of intrinsic brain function converged on common loci of dysfunction in ASD (mid and posterior insula, posterior cingulate cortex), and highlighted less commonly explored regions such as thalamus. The survey of the ABIDE R-fMRI datasets provides unprecedented demonstrations of both replication and novel discovery. By pooling multiple international datasets, ABIDE is expected to accelerate the pace of discovery setting the stage for the next generation of ASD studies.
Keywords

Resting state fMRI; Intrinsic functional connectivity; Data sharing; Large-scale networks; Default network; Interhemispheric connectivity; Thalamus

INTRODUCTION

Autism spectrum disorders (ASD), formerly considered rare, are now reported to occur in ~1% of children.\textsuperscript{1, 2} Increased recognition of ASD derives at least partially from the adoption of standardized methods for their evaluation and diagnosis.\textsuperscript{3, 4} Beyond clinical utility, standardized approaches facilitate comparison and synthesis of findings across research studies. Consistent phenotypic characterizations have also facilitated establishing large open access data repositories to address the genetic bases of ASD.\textsuperscript{5–8} Open sharing of neuroimaging data has not kept pace, despite substantial potential to inform our understanding of the neurophysiological mechanisms underlying autism.

In response, we introduce the Autism Brain Imaging Data Exchange (ABIDE; http://fcon_1000.projects.nitrc.org/indi/abide/) – a grassroots consortium effort dedicated to aggregating and sharing previously collected resting-state fMRI (R-fMRI) datasets from individuals with ASD and age-matched typical controls (TC). The focus on R-fMRI was motivated by multiple factors. First, ASD neuroimaging studies have increasingly converged on abnormalities in connectivity among brain regions, rather than local functional or structural abnormalities.\textsuperscript{9–11} Second, R-fMRI approaches are particularly suitable for examining intrinsic functional connectivity (iFC); beyond robust test-retest reliability,\textsuperscript{12, 13} R-fMRI sidesteps the challenge of designing tasks capable of probing the wide range of intellectual and behavioral capabilities characteristic of ASD.\textsuperscript{14} Third, as recently demonstrated by the 1000 Functional Connectomes Project\textsuperscript{15} and recent efforts from the International Neuroimaging Data-sharing Initiative (INDI; e.g., ADHD-200)\textsuperscript{16–18} R-fMRI datasets from multiple imaging sites can be fruitfully aggregated for discovery and replication.\textsuperscript{18, 19}

In conceptualizing ABIDE, we hypothesized that the ASD community’s adoption of standardized protocols would be reflected in the sample. Specifically, despite lack of prior coordination, we expected comparable phenotyping across sites due to the widespread use of Autism Diagnostic standardized instruments.\textsuperscript{3, 4} We also anticipated identifying factors that vary across studies, whether by design or unintentionally, to guide future efforts to increase harmonization among research groups.

Another goal was to demonstrate the utility of the aggregated sample for exploring the functional connectome in ASD. Despite overall convergence among R-fMRI studies in supporting a dysconnectivity model of ASD, reports disagree regarding the specific nature and extent of ASD-related abnormalities in iFC (e.g., hypo vs. hyperconnectivity) and the breadth of the systems affected.\textsuperscript{20, 21} In the present work, we carry out a full-brain examination using parcellation-unit based correlation analyses to determine relative prevalence of ASD-related increases vs. decreases in iFC. Given the focus in the ASD
literature on the default network, we also examined voxel-wise iFC for its key components.

Finally, we explored regional iFC dysfunction using four voxel-wise R-fMRI measures, regional homogeneity (ReHo), voxel-matched homotopic connectivity (VMHC), degree centrality (DC), and fractional amplitude of low frequency fluctuations (fALFF). Neither fALFF, a direct index of the spontaneous signal fluctuations underlying resting-state functional connectivity, nor DC, a graph-based measure of the functional relationships of each voxel within the whole connectome, have been examined previously in ASD. These approaches are suited for discovery science thanks to their relative computational simplicity, lack of requirements for data reduction, or a priori knowledge.

METHODS

Contributions

Initial contributions were sought from members of the ADHD-200 Consortium conducting autism research (Kennedy Krieger Institute, NYU Langone Medical Center, Oregon Health & Science University, University of Pittsburgh). Invitations to participate were extended based on personal communications, recent publications and conference presentations. All investigators willing and able to openly share previously collected awake R-fMRI data from individuals with ASD and age- and sex-group matched TC were included. Institutional Review Board (IRB) approval to participate, or explicit waiver to provide fully anonymized data, was required prior to data contribution.

All contributions were based on studies approved by local IRBs, and data were fully anonymized (removing all 18 HIPAA protected health information identifiers, and face information from structural images). All data distributed were visually inspected prior to release.

Phenotypic Data

Prior to data aggregation, consortium members agreed on a “base” phenotypic protocol by identifying overlaps in measures across sites. These included age at scan, sex, IQ, and diagnostic information. Contributors were encouraged to provide as many additional measures as possible, although such contributions were not required given the voluntary, unfunded nature of this effort.

Quality Assurance—Upon receipt, data were checked for extreme outliers (relative to each site’s group), impossible data entries (e.g., beyond published maxima and minima) and missing values. Phenotypic variable entries (e.g., diagnosis) were recoded as necessary to ensure uniformity across sites. Prior to distribution of quality-controlled data, each site reviewed and verified its accuracy. Missing data were imputed for each sample separately, based upon individuals of the same diagnostic category, if the variable was present across ≥60% of datasets and sufficient data were available (i.e., for ≥75% of participants in each diagnostic group at that site). Categorical variables were imputed using the mode and continuous variables using the mean per diagnostic group, per site. When missing, full IQ

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(FIQ) was estimated by averaging available performance and verbal IQ scores per diagnostic
group, per site.

Surveying Group Characteristics—For continuous variables, we calculated range,
mean and SD for each diagnostic group per and across sites. Similarly, for categorical
variables (e.g., diagnosis per fourth and text revised edition of the Diagnostic and Statistical
Manual of Mental Disorders [DSM-IV-TR]), we computed totals and percentages by
diagnostic group.

Imaging Analyses

Sample Selection—Imaging analyses were limited to: 1) males, as they represented 90% of
the aggregate sample, 2) sites with IQ estimated for >75% per diagnostic group, 3)
individuals with FIQ within two SD of the overall ABIDE sample mean (108±15), 4)
individuals with mean framewise displacement (FD) less than two SD above the sample
mean (0.23±0.27mm; Supplementary Figure 1), 5) data with anatomical images providing
near-full brain coverage and successful registration, 6) sites with at least 10 participants per
group after the above exclusions. This yielded data for 763 individuals (ASD=360, TC=403)
from 17 sites; (Supplementary Table 1).

Analytic Strategy—While the ASD literature converges on the presence of abnormal
functional connectivity,9,11 findings of hyper vs. hypoconnectivity vary across studies.20 To
understand the relative contributions of hypo and hyperconnectivity in ASD, we carried out
whole-brain iFC analyses for both structural and functional parcellation schemes (i.e.,
structural: Harvard-Oxford Atlas34, functional: Crad-20035). Whole-brain voxelwise iFC
analyses were computationally impractical given the sample size. Beyond whole-brain
analyses, we focused on regional voxel-wise measures of intrinsic functional architecture
including seed-based iFC of the Default Network,26 ReHo,27,36 VMHC,37 fALFF,32 and
DC.30,31,38 See Supplementary Information.

Image Preprocessing—R-fMRI scans were preprocessed with an alpha version of the
Configurable Pipeline for the Analysis of Connectomes (C-PAC, http://fcp-
indi.github.com/C-PAC/). Image preprocessing steps included slice-timing and motion
correction, nuisance signal regression (including 6 motion parameters, 5 CompCor
signals39 and linear trend) and temporal filtering (0.009–0.1Hz; except for fALFF). Derived
R-fMRI measures were normalized to Montreal Neurological Institute (MNI)152
stereotactic space (2mm isotropic) with linear and non-linear registrations and spatially
smoothed (applied FWHM=6mm). For VMHC analysis, functional data were registered to a
symmetric template.

Whole-Brain iFC Analyses—For each parcellation scheme, we extracted the mean time-
series for each unit from the preprocessed 4D time-series data in MNI space, and then
calculated the full-brain connectivity matrix using Pearson correlation. Correlation
coefficients were Fisher transformed to Z-scores to ensure normality. To facilitate data
characterization and interpretation, we sorted connections based upon lobar (i.e., frontal,
temporal, parietal, occipital, subcortical) and functional40 (i.e., heteromodal, unimodal,
primary somatosensory, paralimbic, limbic, subcortical) classifications. Additionally, following prior results, we sorted findings based on hemispheric configuration (intrahemispheric, homotopic, heterotopic) using the structural parcellation (Crad-200 does not provide explicit homotopic regions).

Regional Measures—The following voxel-wise regional metrics were generated for each participant: 1) ReHo, which represents the average Kendall’s Tau correlation between a given voxel’s time-series and its 26 adjacent neighbors, 2) VMHC, which represents the correlation between a voxel and its opposite hemisphere counterpart on a symmetric template, 3) fALFF, a frequency domain metric reflecting the ratio between the amplitude of fluctuations in the 0.01–0.1 Hz band and the total amplitude within the sampled periodogram, and 4) DC, a measure of the connectome graph indexing the number of direct connections for a given node.

Default Network iFC—To demonstrate the utility of the large-scale aggregate dataset in testing existing hypotheses, we conducted a targeted seed-based correlation examination to test previous suggestions of default network hypoconnectivity in ASD. We focused on its midline core, using spherical region-of-interest masks (radius=4mm) centered at anterior medial prefrontal cortex, and posterior cingulate. For each seed region, a Fisher’s Z-transformed correlation map was generated.

Group-level Analyses—We employed a general linear model implemented in DPARSF to examine neuroimaging differences related to diagnosis (covariates: age, FIQ, site, and mean FD). To correct for multiple comparisons at the cluster level we employed Gaussian random field theory (voxel Z>2.3, cluster-level p<0.05). For parcellation-based whole brain correlation analyses, we corrected for multiple comparisons using false discovery rate (FDR; q<0.05).

Secondary Analyses: ‘Scrubbed’ Data—Given the potential for spurious signal changes from head micromovements, primary analyses accounted for group differences in micromovements by covarying for mean FD at the group-level. To verify the effectiveness of this approach, we repeated analyses after removing frames with FD>0.2mm (‘scrubbing’); individuals with greater than 50% of their time-series removed were excluded from analyses. fALFF was not calculated with ‘scrubbed’ data as the removal of time-points disrupts the temporal structure precluding standard Fourier transform-based approaches.

Structural Analyses—Although beyond this work’s scope, to demonstrate the ability to conduct structural analyses using ABIDE datasets, we computed total intracranial, white matter, gray matter and cerebrospinal fluid volumes; no significant group differences emerged (Supplementary Figure 2 and Information).
RESULTS

Sample Composition

Seventeen sites (Figure 1A, Supplementary Table 2) contributed 20 previously collected datasets for 1112 individuals (533 with ASD, 579 TC); 10 datasets (58%) were previously unpublished in regard to ASD vs. TC R-fMRI comparisons. Contributions per site ranged from 13 to 79 participants with ASD and 13 to 105 TC. Marked variation in age-range across samples was evident along with a vast predominance of males, with 25% of sites excluding females by design (Figure 1B, Supplementary Table 2). With few exceptions, sites included individuals with average or above-average intelligence. Mean FIQ exceeded 100 for TC for all sites and in 17 of 20 datasets for individuals with ASD. Sites varied with respect to the minimum FIQ included (ASD: 41–95; TC: 73–101; Figure 1D); Full and verbal IQ were significantly greater for TC than ASD (p < 0.0001) and so was performance IQ, though it only differed marginally (p=0.067). Right-handedness was more frequent in TC than ASD (p < 0.002). The male-only sample included for imaging analyses reflected these characteristics (Supplementary Tables 1 and 3).

Sites reached ASD diagnoses by either 1) combining clinical judgment and “gold standard” diagnostic instruments – Autism Diagnostic Observation Schedule (ADOS) and/or Autism Diagnostic Interview – Revised (ADI-R) (n=13 samples, 65% of datasets)3, 2) clinical judgment only (n=3, 15%), or 3) “gold standard” diagnostic instruments only (n=4, 20%). Among the 17 sites employing the ADOS and/or ADI-R, 16 (94%) obtained research-reliable administrations and scorings. Site-specific details are available at http://fcon_1000.projects.nitrc.org/indi/abide. Given participant ages (> six years) and IQ, most were evaluated with ADOS Modules 3 or 4. Average ADOS total scores were similar across sites, suggesting consistency in ASD severity.

Calibrated severity scores (computed using the new ADOS algorithm for Modules 1, 2, and 350), were available for nine sites and confirmed this pattern. DSM-IV-TR diagnostic subtypes were provided by 80% of sites. Consistent with previous findings,3 sites differed substantially in subtype (Autism, Asperger Disorder, PDD-NOS) distributions (Figure 1F, Supplementary Tables 1 and 3).

Imaging Findings

Whole-Brain iFC—Regardless of parcellation scheme (structural/functional), we found both hypo and hyperconnectivity in ASD, though with a striking predominance of hypoconnectivity (Figure 2). Analyses sorting abnormal iFC based on functional hierarchy40 showed decreased cortico-cortical iFC across all functional divisions, though in varying degrees (omnibus χ²=33.5, p<0.0001), with paralimbic and unimodal association regions having the highest proportions of affected connections (Figure 2; Supplementary Table 4). Lobar-based classification suggested hypoconnectivity in all lobes, but particularly for the temporal (Supplementary Table 5). ASD-related hyperconnectivity was limited to subcortical regions, particularly for iFC between subcortical (thalamus, globus pallidus) and primary parietal sensorimotor regions; (Figure 2, Supplementary Tables 4 and 5). Finally, examining hemispheric schemes41 revealed ASD-related iFC decreases particularly in
homotopic iFC (Figure 2A dorsal and coronal views; Supplementary Table 6). This pattern of results remained largely unchanged after ‘scrubbing’ - consistent with recent work\cite{18, 49} suggesting that including mean FD as a group-level covariate provides findings similar to scrubbing (Supplementary Figure 3 and Information).

**Regional Abnormalities**—Figure 3 shows brain regions exhibiting significant group differences in regional metrics. We highlight regions exhibiting convergence in ASD-related differences among measures, suggesting more pervasive disturbances in ASD (Figure 4). Two clusters exhibited ASD-related abnormalities in three measures. The first extended from the left posterior insula to the central and parietal operculum and exhibited ASD-related decreases in VMHC, ReHo, and DC. The second cluster was located in right dorsal superior frontal cortex and exhibited ASD-related increases in fALFF, ReHo, and DC. A distributed set of regions exhibited ASD-related reductions in at least two measures, including thalamus, posterior cingulate, bilateral mid-insula, and left middle occipital gyrus. Again, these findings were largely unchanged after ‘scrubbing’ (Supplementary Figure 4).

**Focus on the Default Network**—Seed-based correlations confirmed previous findings of ASD-related default network hypoconnectivity.\cite{23, 25, 42–44} Specifically, we noted decreased long-distance iFC between its anterior and posterior components. We also found decreased iFC between each of the default network components and their neighboring regions (e.g., posterior cingulate and precuneus; anterior medial and dorsomedial prefrontal cortex). Decreases in long-distance iFC were robust to the specific motion-correction employed (‘scrubbing’, group-level correction). In contrast, ASD-related decreases in local iFC were less robust; they were detectable for posterior cingulate, but not for medial prefrontal cortex in secondary analyses using ‘scrubbed’ data (Supplementary Figure 4).

**Site-Related Variation**—Based on prior work,\cite{15} the ability to detect ASD-related differences in the ABIDE sample does not imply a lack of site-related variation. Although not a primary focus of this study, we present a demonstration of site-related variation and a parametric analysis of the impact of sample size on detectable differences for a representative finding (i.e., left insula VMHC; Supplementary Figures 5, 6 and Information).

**Normality**—Reflective of common-practice, the present work employed parametric statistics. Supplementary Figure 7 demonstrates regional variation in the degree to which assumptions of normality are maintained. Non-parametric confirmatory analyses conducted at the cluster level supported results of primary analyses (Supplementary Table 7). Future work may benefit from exploring voxel-wise non-parametric approaches, when normality assumptions are violated (Supplementary Figure 8 and information).

**DISCUSSION**

The feasibility of establishing ABIDE, a collection of 20 mostly unpublished samples from 17 independent sites, testifies to the rapid adoption of R-fMRI approaches to ASD as well as to the benefits of diagnostic harmonization in ASD. Our initial analyses of the ABIDE R-fMRI data replicate and extend key findings in ASD, and highlight emerging significant themes that merit further study.
Whole-brain connectivity analyses reconciled seemingly conflicting evidence of hypo and hyperconnectivity,\textsuperscript{20, 24, 51, 52} by revealing both phenomena in ASD, though to different degrees and with distinct topographies. Specifically, while findings of hyperconnectivity in ASD were limited and primarily associated with subcortical regions, ASD-related hypoconnectivity dominated cortico-cortical iFC. Of note, while ASD-related decreases in iFC extended across functional cortical divisions, there was a predilection for unimodal association areas and paralimbic circuits. The prominence of unimodal association areas is in line with the autism literature, which has consistently implicated the fusiform gyrus,\textsuperscript{53} and superior temporal gyrus.\textsuperscript{54} Likewise, the implication of paralimbic areas is consistent with studies highlighting ASD-related dysfunction within higher order circuits subserving social, cognitive and affective processes.\textsuperscript{21, 25} Findings of ASD-related decreases in iFC within the default network midline core further amplify this theme.

Our results also underscore another emerging theme: alterations in interhemispheric connectivity.\textsuperscript{10, 28, 29, 55–59} Structural morphometric abnormalities (e.g., volume,\textsuperscript{10, 56, 57} microstructure\textsuperscript{55, 59–61}) in the corpus callosum first drew attention to ASD-related interhemispheric dysconnections. While initial volumetric studies only found evidence of partial compromise of the corpus callosum, diffusion tensor imaging studies of corpus callosum microstructure have suggested abnormalities extending to all major subdivisions.\textsuperscript{59, 61} Similarly, while initial R-fMRI studies reported abnormalities in interhemispheric iFC for sensorimotor and language areas,\textsuperscript{28, 29} whole-brain analyses suggest broader compromises, affecting 30% of homotopic connections, across functional hierarchies or lobes. Given that interhemispheric interactions are thought to facilitate high-load cognitive processes,\textsuperscript{62} findings of altered connectivity extending across systems may be relevant to models emphasizing impairments of complex reasoning and information processing in ASD.\textsuperscript{63} Intriguingly, the present work also highlighted decreases in voxel-wise interhemispheric iFC of subcortical areas, suggesting that callosal abnormalities may not exclusively account for abnormal interhemispheric interactions in ASD.

A concern in R-fMRI studies is that requirements for \textit{a priori} information (e.g., seed-specification; number of components in independent component or cluster analyses) influence results. By applying a broad array of unbiased regional metrics, we successfully recapitulated some of the most commonly cited loci of dysfunction (e.g., insula,\textsuperscript{64–66} PCC\textsuperscript{23, 42, 67–69}). Findings of abnormal iFC also converged on a less commonly considered region - the thalamus. While initial R-fMRI studies tended to focus on large-scale cortico-cortico networks,\textsuperscript{23, 42} recent work has emphasized examination of subcortical functional circuits (e.g., cortico-striato-thalamo-cortical circuitry).\textsuperscript{52, 70} The role of these circuits in both sensory-motor processes and learning – fundamental mechanisms that may underlie the pervasive clinical impairments in ASD – make them appealing targets for future studies. Beyond the added value of extending the scope of circuits examined in ASD, unprecedented findings of abnormal fALFF in ASD highlight the need to investigate properties of the intrinsic brain beyond functional connectivity. Supporting this notion, recent work suggests that examination of intrinsic fluctuations in the BOLD signal may provide a window into more fundamental neuronal signatures of ASD.\textsuperscript{71, 72}
Along with the substantial statistical power afforded by the ABIDE aggregate sample, we also note remaining challenges for the field. In particular, the relationships of IQ to psychiatric disorders and brain structure and function are always complex, and the same holds for our sample. Across sites, the ASD and TC groups both tended to cluster around the average to above-average range of FIQ; however, marked between-site variation was noted in the range, mean values, and SD – particularly for individuals with ASD. Future work will need to attend even more closely to IQ, as R-fMRI studies allow the inclusion of individuals with substantially lower IQ than task-based approaches. Beyond IQ, we observed notable variation in the specific diagnostic subtypes reported across studies. Such heterogeneity in presentations of ASD must be considered when generalizing findings from an individual study to the larger literature. Revisions proposed for DSM-5 offer the promise of increasing the accuracy with which heterogeneity in ASD is characterized.

The present findings of ASD-related differences in intrinsic functional architecture despite variations in age across sites suggest that some aspects of the neural signatures of ASD remain constant throughout brain maturation. Yet, mirroring the architectural properties observed in early childhood, evidence of cortico-cortical hypoconnectivity and subcortico-cortical hyperconnectivity suggest maturational abnormalities in ASD. As only a few ABIDE sites spanned childhood to middle adulthood, a definitive examination of the developing brain in ASD is beyond the scope of the present work. Future efforts need to delve into the ascertainment of the developmental dynamics of autism. Including younger ages is a must for such efforts. A meta-analysis of the task-based autism imaging literature in 2009 found that most studies at the time were conducted in adults. The greater representation of children, albeit above 6, in the ABIDE sample suggests that R-fMRI facilitates the examination of neural circuitry at younger ages. Still, the first six years of life represent a critical period in neurodevelopment. Further, initial presentations and diagnosis of ASD extend down to as early as 24 months. With rare exceptions, early development is poorly represented in the neuroimaging literature. As the field moves towards a more comprehensive understanding of the neural basis of ASD and their developmental trajectories, a shift towards imaging toddlers and preschoolers is unavoidable – particularly if imaging is to strive for clinical utility.

Future efforts should also focus on standardized phenotyping, including and extending diagnostic assessments. This will allow comprehensive characterization of dimensional brain-behavior relationships. In addition, physiologic measurements capable of indexing ASD-related abnormalities in brain function should be considered (e.g., eye tracking). Finally, it must be acknowledged that while studies establishing the test-retest reliability for R-fMRI have alleviated concerns about the uncontrolled nature of rest, potential concerns remain that group-differences in mental states associated with the magnet environment (e.g., anxiety) can contribute to findings. Future efforts examining the unique signatures of differing mental states in R-fMRI data should be encouraged.

In summary, the construction and open release of the ABIDE sample represents a landmark milestone in autism imaging. Bringing together international datasets, the ABIDE sample allows for replication, secondary analyses and discovery efforts, as demonstrated in the...
present work, and provides insights into study designs for the next generation of investigations using multifaceted databases such as NDAR rapidly growing in size.  

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. ABIDE Sample Characteristics

(A) Total number of participants per group (green=Typical Controls [TC], purple=Autism Spectrum Disorders [ASD]) for each contributing site ordered as a function of sample size (labeled alphabetically, see Supplementary Table 2 for label key). The same site labels are used for Figures 1 B-F. (B) Number of males (blue-white) and females (red) for each site irrespective of diagnostic group (groups were matched for sex). (C) Age (in years) for all individuals per site (ordered by youngest age included per site) irrespective of diagnostic group (groups were age matched). Each site’s mean is represented as a solid red line; the median age across sites (14.7 years) is depicted with a thick red dashed line; 25th, 75th, and 90th percentiles (11.7, 20.1, and 28.3 years, respectively) are represented by thin red dashed lines. (D) Distribution of full IQ (FIQ) standard scores per site (ordered by lowest FIQ included per site) for individuals with ASD (purple, left plot) and TC (green, right plot), respectively. Solid black lines indicate mean FIQ per site. (E) The Tukey box-whiskers plots depict the distribution of Total Autism Diagnostic Observation Scale (ADOS) scores (i.e., sum of scaled Communication and Reciprocal Social interaction subtotals) for individuals with ASD in the 13 sites using the ADOS. (F) Number of probands assigned to specific ASD diagnostic categories per site. Categories were DSM-IV-TR Autistic Disorder (red), Asperger Syndrome (aqua green), and Pervasive Developmental Disorder—Not Otherwise Specified (PDD-NOS) (white-gray pattern), and individuals identified as ASD but not further differentiated into specific DSM-IV-TR subtypes (gray). Data displayed in D and E were imputed as described in main text.

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Figure 2. Whole-Brain Intrinsic Functional Connectivity (iFC) Analyses

(A) Significant group differences (i.e., Autism Spectrum Disorders [ASD] vs. Typical Controls [TC]) for iFC between each of the 112 parcellation units (56 per hemisphere) included in the structural Harvard-Oxford Atlas (HOA). Parcellations are represented with their center of mass overlaid as spheres on glass brains. The upper panel shows the intrinsic functional connections (blue lines) that were significantly weaker in ASD vs. TC. The lower panel shows the intrinsic functional connections that were significantly stronger in ASD relative to TC (red lines). Each HOA unit is colored based on its membership in the six functional divisions per Mesulam et al. [yellow=primary sensorimotor (SM); green=unimodal association; blue=heteromodal association; orange=paralimbic; red=limbic; pink=subcortical]. Interhemispheric iFC is noted on dorsal and coronal views. Glass brains (left lateral, dorsal, and coronal views, shown from left to right) are generated using BrainNet Viewer (http://www.nitrc.org/projects/bnv/). Displayed results are corrected for multiple comparisons using false discovery rate (FDR) at p<0.05. (B) The table summarizes the absolute number and percentage of node-to-node iFC surviving statistical threshold for group comparisons within and between functional divisions. Gray cells represent absence of significant iFC, blue cells represent ASD-related hypoconnectivity (Hypo: ASD<TC), while red cells represent hyperconnectivity (Hyper: ASD>TC). Blue and red shadings decrease proportionally from the highest percentage (37%) to the lowest (~0%). See Supplementary Tables 4, 5 and 6 for results based on lobar and hemispheric divisions as well as for those based on the Crad-200 functional parcellation and Supplementary Information for further discussion on the approach.
Figure 3. Regional Measures of Intrinsic Functional Architecture

(A) Z maps of the grand means (i.e., across all 763 individuals) and (B) significant group differences between individuals with Autism Spectrum Disorders (ASD) and Typical Controls (TC) for each of the four regional measures examined. These were fractional amplitude of low frequency fluctuations (fALFF), regional homogeneity (ReHo), voxel-mirrored homotopic connectivity (VMHC), and degree centrality (DC). We employed Gaussian random field theory to carry out cluster-level corrections for multiple comparisons (voxel-level $Z > 2.3$; cluster significance: $p < 0.05$, corrected). Significant clusters are overlaid on inflated surface maps generated using BrainNet Viewer (http://www.nitrc.org/projects/bnv/), as well as on axial images generated with REST Slice Viewer (http://www.restfmri.net). L= Left hemisphere; R= Right hemisphere.
Figure 4. Overlap Between Regional Measures of Intrinsic Brain Function

(A) Surface and axial maps depict the extent of overlap for significant group differences (i.e., Autism Spectrum Disorders [ASD] vs. Typical Controls [TC]) among any of the four regional measures of intrinsic brain function shown in Figure 3. Purple clusters represent areas of significant group differences emerging for only one measure; orange and yellow clusters indicate measures with overlap among 2 and 3 measures, respectively. (B) For each of the yellow and orange clusters in panel A, the table lists the cluster’s anatomical area label, cluster size in number of voxels, and stereotaxic coordinates for the center of mass in Montreal Neurological Institute (MNI) coordinates, the specific measures involved in the overlap, and the group difference direction (ASD>TC in red, ASD<TC in blue). L= Left hemisphere; R= Right hemisphere.
Figure 5. Seed Based Correlation Analyses: Default Network

(A) Z maps of the grand means (i.e., across all 763 individuals) and (B) of the group differences between individuals with Autism Spectrum Disorders (ASD) and Typical Controls (TC) for the two midline core seed regions located in Posterior Cingulate Cortex (PCC) and Anterior Medial Prefrontal Cortex (aMPFC). Seeds were centered at Montreal Neurological Institute stereotaxic coordinates x=−8, y=−56, z=26 for PCC and x=−6, y=52, z=−2 for aMPFC, and are depicted as white dots on the surface maps. Gaussian random field theory was used to carry out cluster-level corrections for multiple comparisons (voxel-level Z>2.3; cluster significance: p<0.05, corrected). Significant clusters are overlaid on inflated surface maps generated using BrainNet Viewer (http://www.nitrc.org/projects/bnv/), as well as on axial images generated with REST Slice Viewer (http://www.restfmri.net). L= Left hemisphere; R= Right hemisphere.