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Connectome-wide Mega-analysis Reveals Robust Patterns of Atypical Functional Connectivity in Autism

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ABSTRACT

BACKGROUND: Neuroimaging studies of functional connectivity (FC) in autism have been hampered by small sample sizes and inconsistent findings with regard to whether connectivity is increased or decreased in individuals with autism, whether these alterations affect focal systems or reflect a brain-wide pattern, and whether these are age and/or sex dependent.

METHODS: The study included resting-state functional magnetic resonance imaging and clinical data from the EU-AIMS LEAP (European Autism Interventions Longitudinal European Autism Project) and the ABIDE (Autism Brain Imaging Data Exchange) 1 and 2 initiatives of 1824 (796 with autism) participants with an age range of 5–58 years. Between-group differences in FC were assessed, and associations between FC and clinical symptom ratings were investigated through canonical correlation analysis.

RESULTS: Autism was associated with a brainwide pattern of hypo- and hyperconnectivity. Hypoconnectivity predominantly affected sensory and higher-order attentional networks and correlated with social impairments, restrictive and repetitive behavior, and sensory processing. Hyperconnectivity was observed primarily between the default mode network and the rest of the brain and between cortical and subcortical systems. This pattern was strongly associated with social impairments and sensory processing. Interactions between diagnosis and age or sex were not statistically significant.

CONCLUSIONS: The FC alterations observed, which primarily involve hypoconnectivity of primary sensory and attention networks and hyperconnectivity of the default mode network and subcortex with the rest of the brain, do not appear to be age or sex dependent and correlate with clinical dimensions of social difficulties, restrictive and repetitive behaviors, and alterations in sensory processing. These findings suggest that the observed connectivity alterations are stable, trait-like features of autism that are related to the main symptom domains of the condition.

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Autism spectrum condition (henceforth autism) is a lifelong early-onset neurodevelopmental condition characterized by social communication difficulties, restricted and repetitive behaviors (RRBs), and atypical sensory processing (1). The prevalence of autism is high, with 1%–2% of all people worldwide affected (2). The absence of effective treatments underscores the need to better understand the neural underpinnings of the condition. Over the last 2 decades, the research community has shifted its view from considering autism as a condition of isolated brain regions to investigating the hypothesis that autism is associated with atypical interactions across distributed brain networks (3,4).

Through advances in different network mapping techniques (5–8), recent years have seen an increasing focus on trying to understand how distinct aspects of brain connectivity are altered in individuals with autism. Early work in 2004 examining functional connectivity (FC) in autism reported decreased FC (hypoconnectivity) in individuals with autism relative to neurotypical (NT) control subjects during the performance of a sentence comprehension task (9). Several subsequent resting-state functional magnetic resonance imaging (rs-fMRI) studies also found decreased FC in autism (10–12). In contrast, other rs-fMRI studies have reported increased FC (hyperconnectivity) in autism, including FC between primary sensory and subcortical networks (13), and within the primary motor cortex (14), ventral attention, default mode network (DMN), and visual networks (15). Later studies, published from 2013 to 2019, put forward an even more complex picture, reporting both hyperconnectivity and hypoconnectivity, within and between various brain networks (15–18).

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Some of the atypical FC patterns reported in the literature have been interpreted in different ways. For example, many studies of FC in autism focus on the DMN, although the findings have been mixed (19). Since the DMN has been associated with social cognition and theory of mind (20), altered connectivity within and between the DMN would be consistent with the view that social cognitive deficits represent some of the most fundamental characteristics of autism (21,22). Moving beyond the DMN, evidence for more diffuse changes in FC that span multiple brain systems has been linked to the weak central coherence theory (23), which proposes that people with autism are biased toward processing details as opposed to extracting contextual meaning and seeing the big picture (24).

Accordingly, while many rs-fMRI studies have reported altered FC in autism, these findings are inconsistent with respect to the specific networks implicated and whether these networks show, relative to NTs, increased FC, decreased FC, or a combination of both (25).

Several factors may have contributed to these inconsistencies. First, most studies have relied on small sample sizes, typically $<$70 per group (25), which can inflate effect sizes and decrease the reproducibility of results (26). Multisite consortia such as the ABIDE (Autism Brain Imaging Data Exchange) (18), EU-AIMS LEAP (European Autism Interventions Longitudinal European Autism Project) (27), and ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) (28) have been established to overcome such sample size limitations. Second, many studies differ in terms of whether and how they account for head motion (29–31). Increased head motion can lead to artifactual findings of decreased long-distance FC and increased short-distance FC (32,33), a pattern that has also been hypothesized in autism (34). Third, inconsistent results may also be driven by the different network mapping techniques used. Many studies either use seed-based connectivity, which only allows for investigating a limited number of brain regions (25), or spatial independent component analysis, which has a limited capacity to identify the specific connections between brain regions that may be altered. Finally, the age range of studied samples shows considerable variation, which may affect the results. For example, Uddin *et al.* (35) identified a pattern of hyperconnectivity in children and hypoconnectivity in adolescents and adults across several studies.

In this study, we aim to overcome these limitations by combining data from 3 of the largest initiatives to date: LEAP (27), ABIDE 1, and ABIDE 2 (18). Following rigorous quality control and consideration of motion-related contamination, we combine mega-analytic (i.e., data pooling) methods with comprehensive whole-brain network mapping and analysis techniques analogous to cluster-based inference in fMRI (36) to generate connectome-wide maps of altered FC across 75,855 different connections linking 390 brain regions. Importantly, our total sample spans ages 5–58 years, allowing us to investigate the age dependence of any autism-related changes in FC. We use canonical correlation analysis (CCA) to relate FC alterations in autism to distinct dimensions of clinical symptomatology. Critically, we replicate the results obtained with the whole data in the LEAP and ABIDE 1 and 2 datasets independently.

Our primary goal was to test the hypothesis that autism is associated with both hypo- and hyperconnectivity and to characterize relationships between FC alterations and clinical scores covering the 3 main symptom domains of autism; namely, social difficulties, restricted interests and repetitive behavior, and sensory processing. Our unique approach thus allowed us to comprehensively evaluate the network specificity and polarity of FC alterations in autism, their age dependence, and their clinical correlates.

METHODS AND MATERIALS

Participants

We combined data from 3 large datasets: LEAP (27) (https://www.eu-aims.eu/ and https://www.aims-2-trials.eu/) and ABIDE 1 and ABIDE 2 (18) (http://fcon_1000.projects.nitrc.org/indi/abide/) (see Supplement Section 1).

Our final sample for analysis included 796 individuals with autism (141 females; age range: 5–58 years) and 1028 NT individuals (256 females; age range: 5–56 years). Details about our exclusion criteria are provided in Supplement Section 2. The clinical and demographic characteristics of included participants are listed in Table 1. For age distribution, see Figure S11.

Clinical Diagnosis

Individuals with autism in the LEAP dataset had an existing clinical diagnosis of autism according to the criteria of DSM-IV, DSM-5, or ICD-10, with the majority also meeting the autism criteria on Autism Diagnostic Interview (ADI)-Revised (37) and/or Autism Diagnostic Observation Schedule 2 (ADOS 2) (38) [see Charman, *et al.* 2017 (39)]. Each site within ABIDE followed their individual diagnostic procedures for establishing an autism diagnosis, although the majority of the sites used the ADOS (40) and/or ADI-Revised (37). NT control subjects were individuals that reported no psychiatric diagnosis.

MRI Acquisition and Preprocessing

rs-fMRI and structural scans were obtained using 3T MRI scanners at 32 scanning sites (Supplement Section 3). The Supplement also contains details on denoising efficacy (Supplement Section 4) and the sensitivity of our findings to different preprocessing procedures (Supplement Section 5).

Mapping FC

To investigate autism-related FC alterations across the brain, we applied the well-validated Schaefer parcellation to divide the cortex of each participant into 400 functional regions of interest (ROIs) (41) combined with 15 subcortical ROIs from the Harvard-Oxford subcortical atlas (42). We extracted the mean time series from each ROI and computed the Pearson correlation between every pair of time series. The values within each participant's FC matrix were normalized using Gaussian-gamma mixture modeling (43) (Supplement Section 6). ComBat (44) was used on the FC matrices to remove the confounding effects of scanning site from the fMRI data (Supplement Section 7).

Analysis of Group Differences

Through a mega-analytic approach (the pooling of raw data acquired at multiple sites), we mapped connectome-wide differences between individuals with autism and NT individuals using the Network-Based Statistic (NBS) (36) (software available at http://www.nitrc.org/projects/nbs/). The NBS addresses the multiple comparison problem inherent in connectome-wide analyses by performing statistical inference at the level of connected components, which are sets of nodes that can be linked by a path of edges. The approach thus accounts for topological relations between affected sets of edges, rather than treating each edge individually, offering considerable gains in statistical power at the expense of restricting inferences to the level of edge components rather than individual connections (36). For details about the NBS procedure, see Supplement Section 8. For comparison, we additionally performed an edge-level analysis corrected using false discovery rate with $q < .05$. To assess FC group differences, a general linear model was fitted to each edge, including diagnosis, age, sex, and mean framewise displacement as covariates. We examined interactions between diagnosis and age and diagnosis and sex and additionally considered nonlinear age and age interaction effects (see Supplement Section 9). We report results at a stringent component-wide threshold, familywise error corrected (FWE) for 6 comparisons to $p_{FWE} < .001$, following the application of primary component thresholds corresponding to $p < .05$, .01, and .001 (45).

We used the Yeo 7-network parcellation to assign cortical ROIs to well-known resting-state networks (46). These assignments allowed us to quantify the number of edges identified by the NBS as showing an effect of interest within and between each of the networks (N_{raw}). As the number of ROIs and potential connections within and between networks differs, we also calculated the proportion of altered edges corrected by the total amount of possible edges within or between the particular networks (N_{norm}). Thus, raw counts allow us to identify networks that contribute strongly to group differences in absolute terms; normalized counts allow us to identify strong contributions relative to network size. We also calculated the degree of each region, defined as the number of connections attached to each node in the NBS subnetwork, thus identifying specific regions heavily involved in connectivity differences. To further demonstrate the robustness and replicability of our findings, we conducted full FC mapping and analysis of group differences in the 2 fully independent datasets of the LEAP and ABIDE 1 and 2 initiatives separately. To examine the consistency of our main findings with those obtained following different validation and sensitivity analyses, we used the Dice similarity coefficient (DSC) (47) to quantify the edgewise consistency of the affected networks (i.e., the binary, NBS-derived connectivity alterations matrices) and Pearson correlations of the weighted edge-level matrices and network-level edge-count matrices (Supplement Section 9 and Table S9).

Brain-Behavior Correlations

We used CCA to relate autism-related FC connectivity to symptom severity. In our analyses, one set of variables included measures of behavior and symptom severity, and the other set of measures included principal components (PCs) of the FC estimates for edges identified as showing atypical connectivity in our NBS analysis. We interpreted the results by directly correlating the edge-level measures with the canonical variates (CVs) identified by the CCA, allowing us to determine the contribution of each edge to the CV, providing a clearly interpretable brain-behavior relationship.

We conducted two CCA analyses. In the first CCA, we investigated associations with a diverse set of behavioral variables, including the ADOS social affect (SA), ADOS RRB, ADI RRB, ADI communication, ADI social, Social Responsiveness Scale-2, and Vineland Adaptive Behavior Scale daily living skills, Vineland Adaptive Behavior Scale communication, and Vineland Adaptive Behavior Scale social relationships. These measures were collected across the 3 datasets for a subsample of 232 individuals with autism. Given that the Short Sensory Profile (SSP) scores were available for a smaller sample of 125 individuals with autism and 78 control subjects from the LEAP cohort, we conducted a separate CCA examining FC relationships with the subscales of the SSP (48). The behavioral measures are detailed in Supplement Section 10. We further validated our CCA findings using leave-one-site-out cross-validation as explained in Supplement Section 11.

RESULTS

Atypical FC in Autism

At the primary component-forming threshold of $p < .01$, the autism < NT contrast revealed hypoconnectivity in autism that encompassed 8102 edges (10.6% of the total number of edges) linking 343 brain regions ($p_{FWE} < .001$) (Figure 1A–C). The autism > NT contrast revealed hyperconnectivity in autism, including 10,774 edges (14.2% of the total number of edges; $p_{FWE} < .001$) and linking all 390 brain regions (Figure 1D–F). Thus, nearly all brain regions were implicated in both the hyper- and hypoconnectivity findings in autism.

The highest proportion of hypoconnected edges was present within the somatomotor network ($N_{norm} = 0.25$; $N_{raw} = 1474$), followed by between-network connectivity of the somatomotor with the visual network ($N_{norm} = 0.25$; $N_{raw} = 1182$), and between-network connectivity of the somatomotor and the lateral temporal regions of the DMN ($N_{norm} = 0.12$; $N_{raw} = 821$), the dorsal attention ($N_{norm} = 0.23$; $N_{raw} = 807$), and the salience ($N_{norm} = 0.14$; $N_{raw} = 534$) systems (Figure 1A, B). Accounting for the differences in network size further implicated connectivity between the amygdala and the somatomotor networks ($N_{norm} = 0.3$; $N_{raw} = 94$) (Figure 1A, C).

Atypical hyperconnectivity was predominantly found between the DMN and the rest of the brain, particularly the frontoparietal network ($N_{norm} = 0.34$; $N_{raw} = 1533$) (Figure 1D, E). When accounting for differences in network size, atypical FC between the thalamus and the rest of the brain, and between medial temporal areas and thalamus and striatum, also featured prominently (Figure 1D–F).

At the primary component-forming thresholds of $p < .05$ and $p < .001$, the affected networks were denser and sparser respectively, but a similar pattern of both hypoconnectivity and hyperconnectivity was evident (Figure S3). Results were similar when using global signal regression and when including IQ as

Table 1. Demographic and Clinical Information of Included Participants

	All			EU-AIMS LEAP			ABIDE 1			ABIDE 2		
Characteristics	Autism, *n* = 796	NT, *n* = 1028	Test Value, *p* Value	Autism, *n* = 222	NT, *n* = 200	Test Value, *p* Value	Autism, *n* = 369	NT, *n* = 481	Test Value, *p* Value	Autism, *n* = 205	NT, *n* = 347	Test Value, *p* Value
Female/Male, *n*	141/655	256/772	13.2, .0002[a]	64/158	69/131	1.31, .251	48/321	91/390	4.9, .026[a]	29/176	96/251	12.68, .0003[a]
Age, Years, Mean ± SD	16.2 ± 7.0	15.95 ± 6.9	1.7, .1	18.1 ± 5.7	18.3 ± 5.8	−0.4, .7	17.0 ± 7.8	17.1 ± 7.3	−0.3, .8	14.0 ± 7.0	13.0 ± 5.7	1.931, .0539
Full Scale IQ, Mean ± SD, *n*	106.1 ± 15.8, 777	112.2 ± 12.8, 994	−8.97, <.0001[a]	105.5 ± 15.2, 221	108.5 ± 12.6, 199	−2.2, .028[a]	106.4 ± 16.3, 361	111.4 ± 12.4, 464	−5.0, <.0001[a]	106.1 ± 15.7, 195	115.4 ± 12.7, 331	−7.4, <.0001[a]
Head Motion FD, mm, Mean ± SD	0.079 ± 0.037	0.072 ± 0.033	4.18, <.0001[a]	0.076 ± 0.043	0.069 ± 0.035	1.933, .054	0.081 ± 0.034	0.071 ± 0.031	4.41, <.0001[a]	0.077 ± 0.035	0.075 ± 0.033	0.9, .365
Handedness, Total, Right/Left/ Ambidextrous, *n*	627, 523/73/31	834, 754/56/24	NA	190, 158/26/6	163, 144/15/4	NA	243, 207/30/6	331, 300/25/6	NA	194, 158/17/19	340, 310/16/14	NA
Current Medication Use, *n*	207	21	NA	84	12	NA	85	2		38	7	NA
ADOS Total, Mean ± SD, *n*	6.1 ± 2.5, 503	NA	NA	5.0 ± 2.6, 217	NA	NA	7.0 ± 2.1, 181	NA	NA	6.9 ± 2.0, 105	NA	NA
ADI Social, Mean ± SD, *n*	18.0 ± 6.1, 584	NA	NA	15.7 ± 6.6, 212	NA	NA	19.8 ± 5.3, 255	NA	NA	18.4 ± 5.3, 117	NA	NA
ADI Communication, Mean ± SD, *n*	14.6 ± 5.1, 584	NA	NA	12.9 ± 5.6, 212	NA	NA	15.9 ± 4.5, 256	NA	NA	14.8 ± 4.5, 116	NA	NA
ADI RRB, Mean ± SD, *n*	5.1 ± 2.6, 585	NA	NA	3.9 ± 2.5, 212	NA	NA	6.0 ± 2.5, 256	NA	NA	5.3 ± 2.3, 117	NA	NA
SRS T Score, Mean ± SD, *n*	87.5 ± 30.3, 508	20.6 ± 15.4, 535	45.33, <.0001[a]	85.2 ± 30.2, 178	19.9 ± 14.3, 93	19.74, <.0001[a]	91.0 ± 30.3, 160	21.9 ± 16.8, 165	25.5, <.0001[a]	86.6 ± 30.21, 170	20.0 ± 15.0, 277	31.0, <.0001[a]
VABS Adaptive Behavior Composite, Mean ± SD, *n*	143.0 ± 96.5, 298	247.7 ± 113.4, 107	−9.17, <.0001[a]	73.6 ± 12.2, 187	102.8 ± 10.3, 38	−13.78, <.0001[a]	237.5 ± 39.2, 66	326.6 ± 37.3, 43	−11.8, <.0001[a]	293.1 ± 55.5, 45	329 ± 50.5, 26	−2.7, <.008[a]
VABS Daily Living Skills, Mean ± SD, *n*	79.3 ± 14.9, 298	101.7 ± 11.7, 107	−14.0, <.0001[a]	75.7 ± 15.0, 187	100.3 ± 10.8, 38	−9.58, <.0001[a]	83.3 ± 14.5, 66	104.4 ± 12.7, 43	−7.77, <.0001[a]	87.9 ± 9.8, 45	99.4 ± 10.9, 26	−4.58, <.0001[a]
VABS Socialization, Mean ± SD, *n*	75.5 ± 15.2, 298	108.8 ± 12.0, 107	−20.46, <.0001[a]	73.7 ± 14.9, 187	108.2 ± 11.3, 38	−13.46, <.0001[a]	74.7 ± 15.5, 66	111.7 ± 11.7, 43	−13.35, <.0001[a]	83.9 ± 13.3, 45	104.8 ± 12.7, 26	−6.46, <.0001[a]
VABS Communication, Mean ± SD, *n*	79.4 ± 15.1, 298	105.7 ± 12.6, 107	−16.1, <.0001[a]	78.0 ± 15.0, 187	102.9 ± 12.4, 38	−9.59, <.0001[a]	78.4 ± 14.9, 66	108.2 ± 12.8, 43	−10.79, <.0001[a]	86.6 ± 14.3, 45	105.6 ± 12.1, 26	−5.69, <.0001[a]

ABIDE, Autism Brain Imaging Data Exchange; ADI, Autism Diagnostic Interview; ADOS, Autism Diagnostic Observation Schedule; EU-AIMS LEAP, European Autism Interventions Longitudinal European Autism Project; FD, framewise displacement; NA, not applicable; NT, neurotypical; RRB, restrictive interests and repetitive behavior; SRS, Social Responsiveness Scale; VABS, Vineland Adaptive Behavior Scale.

[a]Statistically significant difference.

a covariate (Supplement Sections 5 and 9), supporting the robustness of our findings. Our conclusions remain unchanged in light of the edge-level false discovery rate–corrected analyses (Figure S16) and sensitivity analyses for sex, medication, and comorbidity with attention-deficit/hyperactivity disorder and the inclusion of participants with IQ < 70. These findings can be found in Supplement Section 9. See Table S9 for a quantitative summary of the results consistency with the main findings across additional analyses.

Age- and Sex-Dependent FC Changes in Autism

We identified marginal evidence for an age-by-diagnosis interaction for the autism $>$ NT contrast ($p_{FWE} = .08$) at the primary threshold of $p < .05$ (Supplement Section 12). No significant sex-by-diagnosis interactions were identified.

Split-Sample Analysis

To further demonstrate the robustness and replicability of our findings, we conducted the full FC mapping and analysis of group differences separately in the LEAP and ABIDE 1 and 2 data.

Our results of an atypical pattern of hyper- and hypoconnectivity were largely consistent when analyzing the LEAP and ABIDE 1 and 2 datasets separately (Figure S15), with the network counts of the two results being highly correlated with our primary findings shown in Figure 1 (LEAP: $r_{network\_hypo} = 0.92$ and $r_{network\_hyper} = 0.89$; ABIDE $r_{network\_hypo} = 0.95$ and $r_{network\_hyper} = 0.98$). The results obtained at the level of individual edges were also consistent, being particularly strong for the ABIDE sample ($r_{edge\_hypo} = 0.95$; $DSC_{hypo} = 0.75$; $r_{edge\_hyper} = 0.94$; $DSC_{hyper} = 0.76$) but somewhat weaker for the LEAP data ($r_{edge\_hypo} = 0.72$; $DSC_{hypo} = 0.36$; $r_{edge\_hyper} = 0.72$; $DSC_{hyper} = 0.37$). Collectively, these results suggest that while different samples may lead to some discrepancies in the specific edges identified as altered, the pattern of differences observed at the level of canonical networks is highly consistent. Further details can be found in the Supplement Section 13, Figure S15.

Brain-Behavior Correlations

We next used CCA to evaluate brain-behavior correlations between 10 behavioral measures and 48 PCs, explaining 50% of the FC variance. This analysis revealed 2 significant CVs (CV1: $r = 0.72$, $p < .0001$; CV2: $r = 0.65$, $p < .0001$) (see Figure 2A, E).

The first CV exhibited a very strong association with the restricted interests and repetitive behavior scale of the ADOS (ADOS RRB; loading = 0.82) (Figure 2B). Analysis of the FC loadings revealed that higher RRB scores were associated with lower FC within the somatomotor network and between this network and the dorsal and ventral attention systems (Figure 2C); higher FC between the DMN and visual network; and higher FC between the DMN and dorsal attention and frontoparietal networks (Figure 2D). Normalized proportions additionally revealed a contribution of lower striatal connectivity with nearly all other systems (Figure 2C) when accounting for network size. Regional degree analysis identified the left nucleus accumbens and the somatomotor cortex as regions with many connections where lower FC was associated with RRBs (Figure 2C), and posterior cingulate and medial frontal cortex as regions where higher FC was associated with RRBs in autism (Figure 2D).

The second CV exhibited a strong association with the ADOS SA score (loading = 0.82) (see Figure 2F). Higher ADOS SA scores were associated with lower connectivity mainly within the somatomotor network and between the somatomotor network and higher-order attentional networks and between the thalamus and somatomotor and attentional networks (Figure 2G). Greater social difficulties were also associated with higher FC between the DMN and the rest of the brain, particularly the visual network (Figure 2H). Higher FC of the cuneus, lingual gyrus, and posterior cingulate cortex was implicated in this relationship (Figure 2H).

In our second CCA analysis, we evaluated brain-behavior correlations between the 6 SSP subscale scores and 44 PCs, explaining 50% of the variance across both control subjects and individuals with autism. This analysis revealed one significant CV (CV1: $r = 0.63$, $p < .0001$) (see Figure 3A). The loadings of CV1 revealed a significant association with sensation seeking (loading = 0.85), visual/auditory sensitivity (loading = 0.72), and movement sensitivity (loading = 0.74) (Figure 3B). Greater sensory sensitivities were associated with lower FC between the visual and somatomotor network and between the amygdala and somatomotor network (Figure 3C), higher FC between the somatomotor and frontoparietal network, and higher FC between the DMN and nearly all other networks, especially the ventral attention and frontoparietal networks. Higher within-network connectivity of the DMN was also associated with atypical sensory processing. Normalized proportions revealed that sensory sensitivities were related to higher FC between the thalamus and the rest of the brain (Figure 3D).

We additionally conducted leave-one-site-out validation analyses, which yielded consistent findings (Figures S12, S13; Tables S12, S13).

DISCUSSION

Using a comprehensive connectome-wide mega-analysis, we report that autism is associated with complex, widely distributed differences in FC that encompass the entire brain. We demonstrated the robustness of these findings through various sensitivity analyses, including successful network-level replication in separate analyses of the LEAP and ABIDE 1 and 2 datasets. Reduced FC is predominantly found within the somatomotor network and between the sensory-motor processing networks and higher-order attentional systems. Increased FC is predominantly found between the DMN, subcortex, and the rest of the brain. These patterns show strong associations with sensory processing difficulties and distinct associations with clinical variables, such that lower connectivity of sensorimotor and attentional networks is associated with social difficulties and restricted interests, and repetitive behaviors, whereas higher FC between the DMN and other systems is mainly associated with social impairments. We found marginal evidence for age-dependent FC changes and no interaction between diagnosis and sex. Our findings thus indicate that autism is characterized by a relatively stable

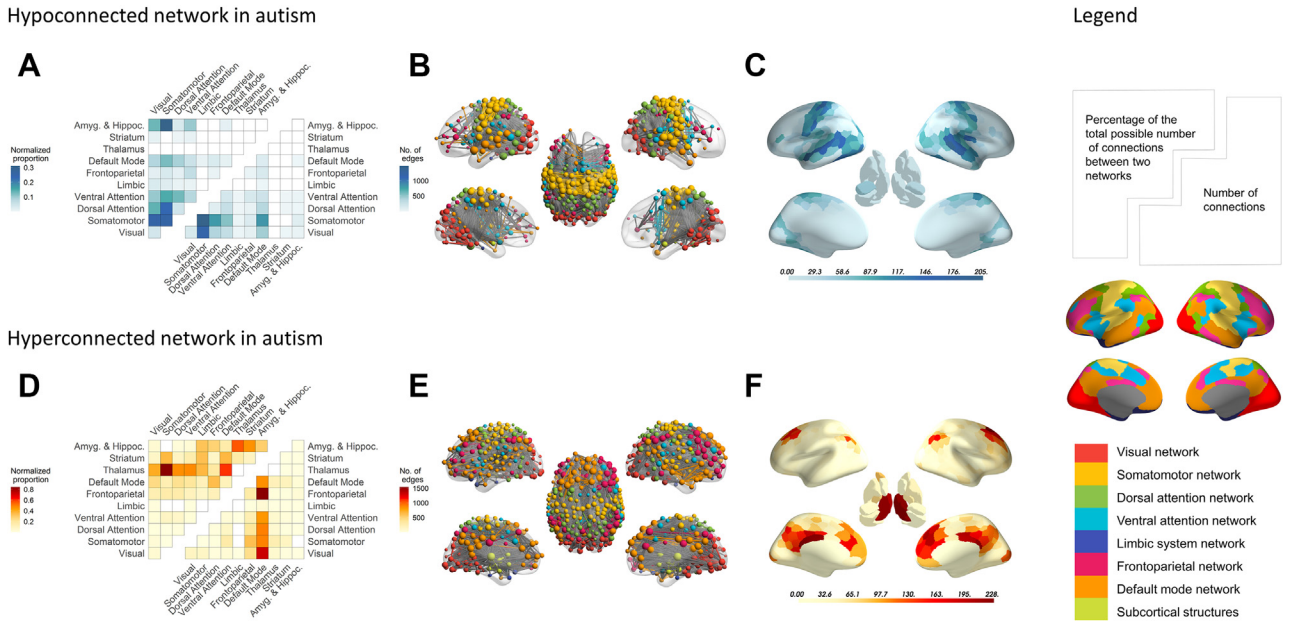

Figure 1. Networks of altered functional connectivity in autism. **(A)** Matrix indicating the number of decreased connections (hypoconnectivity in autism) between and within networks at the primary threshold corresponding to $p < .01$. As indicated in the legend, the upper triangle of the matrix shows the proportion of decreased connections falling within and between each of the networks, normalized by the total number of possible connections within or between the corresponding networks; the lower triangle shows the raw count of edges. The values in these matrices represent the number of edges in the network-based statistic component that falls within each network and between each pair of networks. **(B)** Anatomical projection of the edges showing significant hypoconnectivity in autism. **(C)** Cortical and subcortical maps showing the degree of each region within the network-based statistic-identified hypoconnectivity network in autism. **(D)** Matrix indicating the number of increased connections (hyperconnectivity in autism) between and within networks at the primary threshold corresponding to $p < .01$. As indicated in the legend, the upper triangle of the matrix shows the proportion of increased connections falling within and between each of the networks, normalized by the total number of possible connections within or between the corresponding networks; the lower triangle shows the raw count of edges. **(E)** Anatomical projection of the edges showing significant hyperconnectivity in autism. **(F)** Cortical and subcortical maps showing the degree of each region within the network-based statistic-identified hyperconnectivity network in autism. Amyg., amygdala; Hippoc., hippocampus.

pattern of widely distributed increases and decreases in FC that are related to clinical symptoms of the condition.

Hypoconnectivity in Autism

Our results indicate that hypoconnectivity in autism is most prevalent for functional connections within the somatomotor network and connections linking the visual and somatomotor network to each other and to attentional networks. Several studies have previously reported atypical sensory processing and visual-motor integration in autism (14,49–53). Our finding of hypoconnectivity between the visual and somatomotor network is furthermore consistent with recent work (16) showing lower connectivity among visual association, somatosensory, and motor networks in autism.

The CCA revealed that while lower connectivity within the somatomotor network and between the somatomotor network and the attentional networks is related to RRBs and social difficulties, lower connectivity between the somatomotor network and the visual network is related to 3 subscales of the SSP. The link between altered sensory processing and social impairments and RRBs in autism is supported by the previous literature (54–56). Lower connectivity of the somatomotor cortex has been associated with atypical primary sensory processing, which might potentially hamper the ability to filter relevant information and recruit a suitable motor response, leading to reduced integration of the somatomotor networks with the salience and dorsal attention networks (54). RRBs have been suggested to provide a way to manage atypically regulated sensory stimulation by means of reducing overstimulation or creating stimulation in cases of stimulation seeking (54).

Hyperconnectivity in Autism

Our results further revealed prominent hyperconnectivity within the DMN and between the DMN and the rest of the brain, particularly with the frontoparietal and visual networks in individuals with autism. Thalamocortical connectivity and connectivity between medial temporal and striato-thalamic systems also showed prominent connectivity increases relative to network size. The CCA indicated that the observed pattern of hyperconnectivity, particularly the between-network connectivity of the DMN, was linked to sensory processing difficulties and social impairments (ADOS-SA). FC between the DMN and the visual network was also strongly associated with restrictive and repetitive behaviors and social impairments, whereas FC within the DMN, between the DMN and the ventral attention and frontoparietal networks, was strongly linked to atypical sensory processing.

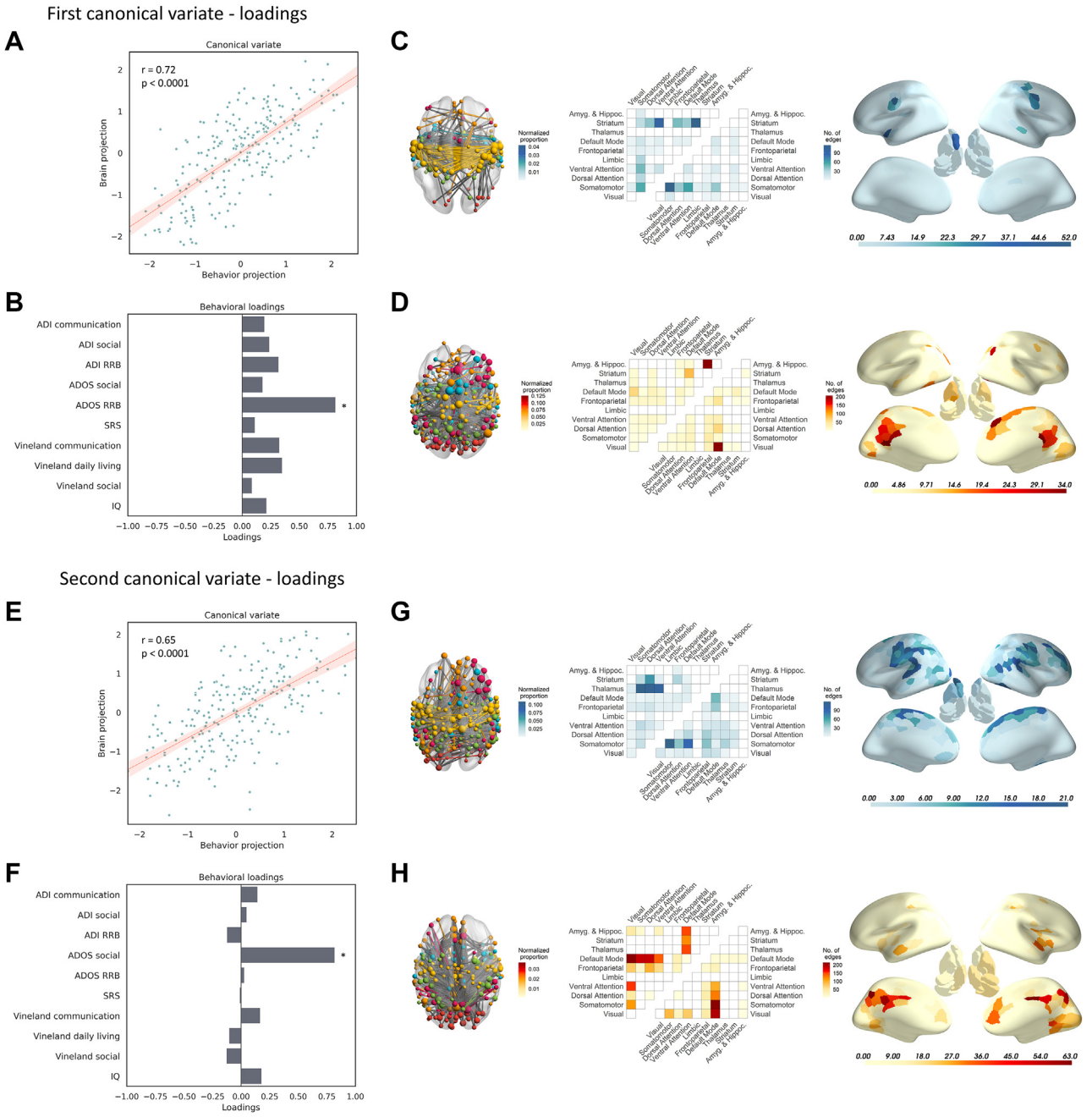

Figure 2. Brain-behavior correlations with respect to the restrictive and repetitive behavior (RRB), adaptive behavior, and IQ scales. **(A)** Correlation of the first pair of canonical variates (CV1: $r = 0.72$, $p < .0001$) resulting from the canonical correlation analysis linking the behavioral scores to the principal components accounting for 50% of the variance in edges with atypical functional connectivity (FC). **(B)** Structural coefficients, also known as loadings of the behavioral scores with the first CV. **(C)** Significant negative correlations of FC with CV1: $p < .05$, characterized at the edge, network and region level. **(D)** Significant positive correlations of FC with CV1: $p < .05$, characterized at the edge, network and region level. **(E)** Correlation of the second pair of canonical variates (CV2: $r = 0.65$, $p < .0001$). **(F)** Structural coefficients, also known as loadings of the behavioral scores with the second CV. **(G)** Significant negative correlations of FC with CV2: $p < .05$, characterized at the edge, network and region level. **(H)** Significant positive correlations of FC with CV2: $p < .05$, characterized at the edge, network and region level. ADI, Autism Diagnostic Interview; ADOS, Autism Diagnostic Observation Schedule; Amyg., amygdala; Hippoc., hippocampus; SRS, Social Responsiveness Scale.

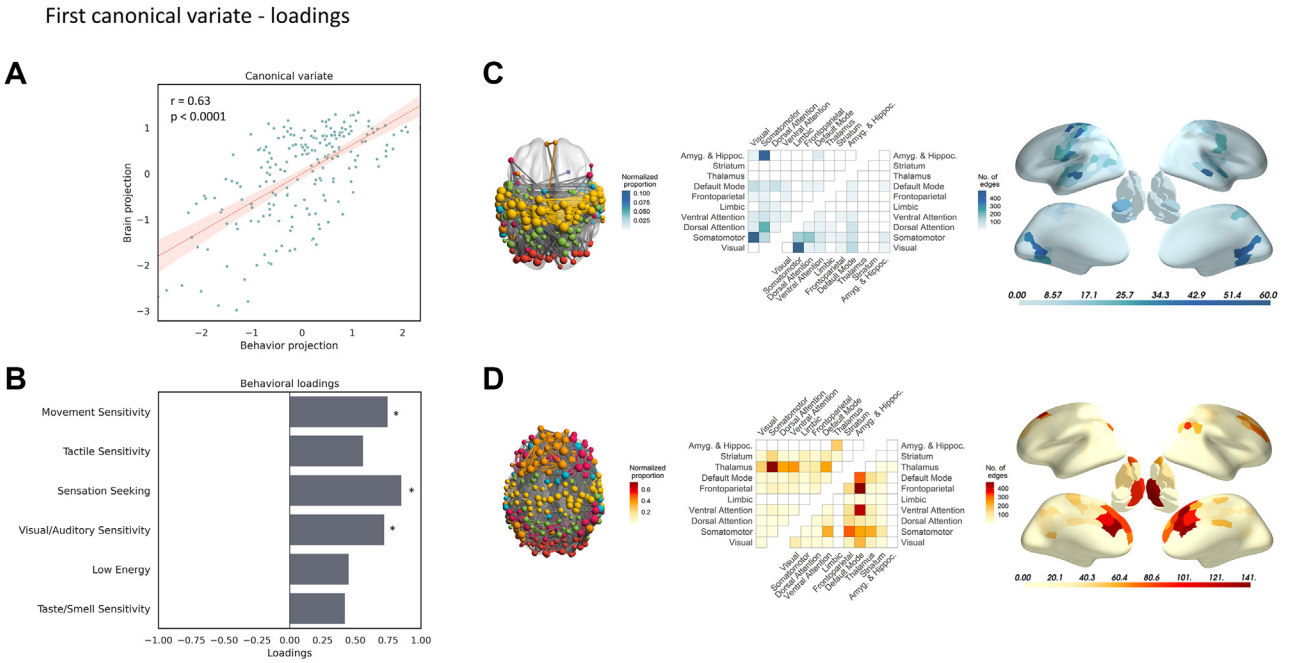

Figure 3. Brain-behavior correlations with respect to the Short Sensory Profile subscales. **(A)** Correlation of the first pair of canonical variates (CV1: $r = 0.63$, $p < .0001$) resulting from the canonical correlation analysis linking the behavioral Short Sensory Profile scores to the principal components accounting for 50% of the variance in edges with atypical functional connectivity (FC). **(B)** Structural coefficients, also known as loadings of the behavioral scores with the first CV. **(C)** Significant negative correlations of FC with CV1: $p < .05$, characterized at the edge, network and region level. **(D)** Significant positive correlations of FC with CV1: $p < .05$, characterized at the edge, network, and region level. Amyg., amygdala; Hippoc., hippocampus.

Our findings accord with many prior rs-fMRI studies implicating disrupted connectivity of the DMN (15,19,57) and disrupted connectivity between the DMN, frontoparietal, and other networks in autism (58,59). Our findings are also consistent with previous work showing increased subcortical-cortical connectivity in autism (13,18,60). Increased connectivity of the frontoparietal network with the DMN and hippocampus might be associated with working memory deficits observed in autism (61–64). The observed associations with social impairments suggest that the general pattern of hyperconnectivity in autism may limit dynamic interactions between networks, potentially leading to decreased behavioral flexibility and thus difficulties in navigating dynamic real-world social situations (15).

The Effects of Age and Sex

We found marginal evidence of an interaction between age and diagnosis, but this result did not survive our significance criteria. Therefore, we did not replicate previously reported findings suggesting developmental effects in autism (35). This may be the result of heterogeneous developmental trajectories in the group of individuals with autism and demonstrates an absence of a robust general developmental trajectory distinguishing the autistic from NT development after the age of 6. We did not observe a significant sex-by-diagnosis interaction, suggesting limited evidence of sexually distinct patterns of altered FC that have been previously observed in autism (65–68). Adequate recruitment of women and girls with autism remains a challenge for the field, and our results require replication in samples with a more balanced male-to-female ratio.

Limitations

Our analysis did not include the cerebellum due to poor scan coverage in many participants. Although our mega-analysis allowed us to examine participants across a relatively broad age range, most participants were under 25 years of age. This is consistent with a general trend in the literature to focus on younger samples. As such, it is still unclear how autism affects the brain beyond the third and fourth decades of life. Our sample sex ratio was imbalanced between the autism and control groups, reflecting the higher proportion of males than females diagnosed with autism in the general population. An important way forward for the field will be to target individuals with autism who are female and particularly those over 30 years of age. Only a small portion of the available subjects had IQ < 70. Further work in such individuals is required to determine whether our results generalize to individuals with autism who are at the lower end of the IQ spectrum. Finally, even though our study shows many significant case-control differences in FC at the group level, these results should be viewed in light of the considerable heterogeneity present across individuals with autism. As such, future work could focus on characterizing heterogeneity in autism and defining autism connectivity subtypes.

Conclusions

Our connectome-wide mega-analysis identified a widespread and robust pattern of altered FC in autism, characterized by prominent hypoconnectivity within sensory processing networks, and between these sensory networks and attentional systems, in addition to hyperconnectivity of the DMN and thalamus, with the rest of the brain. These connectivity differences were associated with distinct clinical dimensions and show limited evidence of age or sex dependence, suggesting that they are stable, trait-like features of autism. Additionally, our network-level findings replicate in 2 independent subsamples. These findings not only reveal a robust pattern of connectivity alterations, but also confirm the importance of both the DMN and sensorimotor systems in the pathophysiology of autism, and highlight their clinical relevance for understanding the symptoms of autism. This work paves the way for further work on discovering connectivity biomarkers and subtypes of autism that will inform clinical practice.

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JKB has been a consultant to/member of advisory board of/and/or speaker for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier in the past 3 years. 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, royalties. TC has served as a paid consultant to F. Hoffmann-La Roche Ltd. and Servier and has received royalties from Sage Publications and Guilford Publications. CFB is the 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 royalities from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press. DGMM 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. The present work is unrelated to the above grants and relationships. All other authors report no biomedical financial interests or potential conflicts of interest.

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