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Archival Report

# Altered Connectivity Between Cerebellum, Visual, and Sensory-Motor Networks in Autism Spectrum Disorder: Results from the EU-AIMS Longitudinal European Autism Project

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## ABSTRACT

**BACKGROUND:** Resting-state functional magnetic resonance imaging–based studies on functional connectivity in autism spectrum disorder (ASD) have generated inconsistent results. Interpretation of findings is further hampered by small samples and a focus on a limited number of networks, with networks underlying sensory processing being largely underexamined. We aimed to comprehensively characterize ASD-related alterations within and between 20 well-characterized resting-state networks using baseline data from the EU-AIMS (European Autism Interventions—A Multicentre Study for Developing New Medications) Longitudinal European Autism Project.

**METHODS:** Resting-state functional magnetic resonance imaging data was available for 265 individuals with ASD (7.5–30.3 years; 73.2% male) and 218 typically developing individuals (6.9–29.8 years; 64.2% male), all with IQ $>$ 70. We compared functional connectivity within 20 networks—obtained using independent component analysis—between the ASD and typically developing groups, and related functional connectivity within these networks to continuous (overall) autism trait severity scores derived from the Social Responsiveness Scale Second Edition across all participants. Furthermore, we investigated case-control differences and autism trait–related alterations in between-network connectivity.

**RESULTS:** Higher autism traits were associated with increased connectivity within salience, medial motor, and orbitofrontal networks. However, we did not replicate previously reported case-control differences within these networks. The between-network analysis did reveal case-control differences showing on average 1) decreased connectivity of the visual association network with somatosensory, medial, and lateral motor networks, and 2) increased connectivity of the cerebellum with these sensory and motor networks in ASD compared with typically developing subjects.

**CONCLUSIONS:** We demonstrate ASD-related alterations in within- and between-network connectivity. The between-network alterations broadly affect connectivity between cerebellum, visual, and sensory-motor networks, potentially underlying impairments in multisensory and visual-motor integration frequently observed in ASD.

*Keywords:* Autism, Cerebellum, Functional connectivity, Resting-state fMRI, Sensory networks, Visual-motor integration

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Autism spectrum disorder (ASD) is an early-onset neurodevelopmental condition affecting 1% to 2% of people worldwide (1). Core behavioral symptoms are impairments in social interaction and communication, the presence of repetitive and restrictive stereotypic behaviors and interests, and atypical sensory processing (2). Yet, symptom presentation and severity vary widely among diagnosed individuals. One key hypothesis is that the diverse symptoms observed in ASD are associated with atypical interactions across distributed brain networks rather than alterations in isolated brain regions (3). This hypothesis is supported by initial task-based functional magnetic resonance imaging (fMRI) studies demonstrating reduced functional connectivity in ASD, suggesting global or long-range hypoconnectivity in ASD (4,5).

However, more recent studies using resting-state fMRI (R-fMRI) to investigate group differences in functional

 
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connectivity yielded more heterogeneous findings [for reviews, see (6–8)]. While several case-control studies reported reduced connectivity in ASD, for example between insula and amygdala (9) or within the default mode network (DMN) (10,11), others demonstrated increased subcortical-cortical connectivity (12,13) or increased connectivity within default mode, salience, motor, and visual networks in ASD (14). Given that increased connectivity was more frequently reported in childhood ASD and decreased connectivity more frequently reported in adulthood ASD, these findings were initially ascribed to developmental effects around puberty (15). Yet, this hypothesis does not accommodate more recent studies reporting functional connectivity increases in certain brain regions but decreases in other areas in both children with ASD (16,17) and adults with ASD (18). These studies indicate that hypotheses of a global increase or decrease in connectivity are likely overly simplistic and that functional connectivity changes in ASD might be network dependent. However, most R-fMRI studies have focused on a limited number of networks, investigating for example only the DMN (19,20) or salience network (21). While contributing to the knowledge of connectivity alterations in ASD, this narrow focus makes it difficult to determine whether observed ASD-related alterations are indeed specific to the networks investigated or reflect a more global change in connectivity. In addition, other methodological differences between studies, such as the use of independent component analysis (ICA)-based versus seed-based approaches and the applied motion correction strategy, might also have contributed to the heterogeneity in findings (6).

More importantly, only a few studies have examined connectivity between different networks in ASD (13,22). Between-network connectivity reflects the integration of information between different networks, which is vital for many functions including perception, learning, and performance of complex cognitive functions, such as social interaction and communication (23,24). The investigation of between-network connectivity might thus reveal important insights into the functional architecture underlying ASD. Indeed, it was recently demonstrated that connectivity between sensory networks and a subcortical and cerebellar network was increased in ASD subjects compared with control subjects (13). While networks underlying sensory processing are relatively underexamined in ASD—likely because atypical sensory processing was only recently added to the DSM-5 diagnostic criteria (2)—these findings highlight the potential significance of between-network connectivity alterations in ASD.

In the present study, we investigated functional connectivity alterations in ASD across the entire brain in 478 participants of the EU-AIMS LEAP (European Autism Interventions—A Multicentre Study for Developing New Medications Longitudinal European Autism Project) (25). Using this large, multicenter dataset including individuals with ASD and typically developing (TD) control subjects across a wide age range (6.9–30.3 years), we aimed to provide a comprehensive, data-driven characterization of ASD-related functional connectivity alterations both within and between 20 different resting-state networks (RSNs). RSNs were obtained using ICA (26) and covered the whole brain, including the sensory networks. Finally, to better capture the phenotypic heterogeneity among ASD and TD participants, we not only compared functional connectivity between the categorically defined ASD and TD groups, but also conducted dimensional analyses relating functional connectivity to a continuous measure of autism trait severity across all participants.

## METHODS AND MATERIALS

### Participants

Participants were part of EU-AIMS LEAP, a large multicenter European initiative aimed at the identification of biomarkers in ASD (25). The study comprised 437 individuals with ASD and 300 TD individuals, both male and female, aged between 6 and 30 years. Participants underwent comprehensive clinical, cognitive, and MRI assessment at one of the following five centers: Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom; Autism Research Centre, University of Cambridge, United Kingdom; Radboud University Nijmegen Medical Centre, the Netherlands; University Medical Centre Utrecht, the Netherlands; and Central Institute of Mental Health, Mannheim, Germany. The study was approved by the local ethical committees of participating centers, and written informed consent was obtained from all participants or their legal guardians (for participants <18 years). For further details about the study design, we refer to Loth *et al.* (27), and for a comprehensive clinical characterization of the LEAP cohort, we refer to Charman *et al.* (25). In the present study, we selected all participants with an IQ >70 for whom a structural and R-fMRI scan were available ($N$ = 553). Participants with a brain abnormality ($n$ = 13; mostly not clinically relevant), an incomplete R-fMRI scan ($n$ = 5; <75% completed), excessive head motion during the R-fMRI scan [$n$ = 43; mean root-mean-square of the framewise displacement ($mean_{FD} > 0.5$) (28)], and insufficient brain coverage ($n$ = 14) were excluded. This resulted in the inclusion of 265 individuals with ASD and 213 TD individuals in our analyses. The clinical and demographic characteristics of these participants are given in Table 1.

### Clinical Measures

Participants in the ASD group had an existing clinical diagnosis of ASD according to the DSM-IV, ICD-10, or DSM-5 criteria. The diagnosis of ASD participants was confirmed using combined information of the Autism Diagnostic Interview—Revised (29) and Autism Diagnostic Observation Schedule 2 (30). We used the total raw score on the Social Responsiveness Scale Second Edition (SRS-2) (31) as a continuous measure for autism traits across all participants since this measure was available for both ASD and TD individuals. The SRS-2 allows assessment of autism traits across clinical and nonclinical samples and includes 65 questions about autistic behaviors, generating scores ranging from 0 to 195, with higher scores indicating more severe impairments. For TD adults, we employed the SRS-2 self-report version (as only the self-report was administered to this group); for all other participants, the parent-report was available. (In Supplemental Table S8, we show that our findings are not dependent on SRS-2 informant).

**Table 1. Participant Characteristics**

| | ASD, $n$ = 265 | | TD, $n$ = 213 | | Test Statistic | Group Difference |
|---|---|---|---|---|---|---|
| Demographic | | | | | | |
| | Mean | SD | Mean | SD | | |
| Age, years | 16.91 | 5.43 | 17.04 | 5.53 | $t_{476} = -0.272$, NS | |
| Full-scale IQ | 103.67 | 16.14 | 108.14 | 14.20 | $t_{476} = -3.172$, $p = .006$ | ASD < TD |
| Head motion during R-fMRI scan, $mean_{FD}$[a] | 0.11 | 0.08 | 0.084 | 0.07 | $t_{476} = 3.024$, $p = .009$ | ASD > TD |
| | $n$ | % | $n$ | % | | |
| Gender, male | 194 | 73.21 | 136 | 63.85 | $\chi^2_1 = 4.531$, $p = .038$ | ASD > TD |
| Handedness, right-handed[b] | 145 | 86.83 | 187 | 82.02 | $\chi^2_2 = 2.273$, NS | |
| Current medication use[c] | 68 | 28.75 | 3 | 2.50 | | |
| Clinical | Mean | SD | Mean | SD | | |
| ADI-R[d] | | | | | | |
| Social Interaction | 16.25 | 6.79 | N/A | N/A | | |
| Communication | 13.14 | 5.57 | N/A | N/A | | |
| RRB | 4.22 | 2.69 | N/A | N/A | | |
| ADOS-2[e] | | | | | | |
| Social Affect | 5.78 | 2.60 | N/A | N/A | | |
| RRB | 4.57 | 2.64 | N/A | N/A | | |
| Total | 5.01 | 2.74 | N/A | N/A | | |
| SRS-2 raw score[f] | 86.13 | 30.99 | 24.78 | 14.49 | $t_{423} = 24.85$[g] | ASD > TD |
| SRS-2 T-score[f] | 69.22 | 12.22 | 45.91 | 5.23 | $t_{423} = 24.23$[g] | ASD > TD |
| ADHD inattentive symptoms[h] | 4.04 | 3.14 | 0.87 | 1.70 | $t_{405} = 9.14$[g] | ASD > TD |
| ADHD hyper/imp symptoms[h] | 2.36 | 2.66 | 0.38 | 1.12 | $t_{405} = 11.91$[g] | ASD > TD |

ADHD, attention-deficit/hyperactivity disorder; ADOS-2, Autism Diagnostic Observation Schedule 2; ADI-R, Autism Diagnostic Interview—Revised; ASD, autism spectrum disorder; FD, framewise displacement; hyper/imp, hyperactivity/impulsivity; N/A, not applicable; NS, not significant; R-fMRI, resting-state functional magnetic resonance imaging; RRB, Restrictive Interests and Repetitive Behavior; SRS-2, Social Responsiveness Scale Second Edition; TD, typically developing.

[a]Motion as measured by the root-mean-square of the mean framewise displacement (28).

[b]Handedness was assessed with the short version of the Edinburgh Inventory (68). Handedness information was available for 167 control participants (left: $n$ = 17, ambidexter: $n$ = 5, right: $n$ = 145) and 228 ASD participants (left: $n$ = 32, ambidexter: $n$ = 9, right: $n$ = 187).

[c]Number of participants taking medication prescribed for behavioral or neurological problems. Medication data was available for 238 ASD and 119 TD participants.

[d]ADI-R (29). Scores were computed for reciprocal interaction (social interaction), communication, and restrictive, repetitive stereotyped behaviors and interests (RRB). ADI-R scores were available for 253 ASD participants.

[e]ADOS-2 (30). Calibrated severity scores were computed for social affect, restricted and repetitive behaviors, and the overall total score. ADOS scores were available for 233 ASD participants.

[f]Total raw and total $T$ score (gender + age normalized) on the SRS-2 (31). SRS-2 scores were available for 416 participants. The raw SRS-2 scores were used in our analyses.

[g]$p < .001$.

[h]ADHD symptoms were assessed with the DSM-5 ADHD rating scale, covering inattention and hyperactivity/impulsivity symptoms [(69); available for 237 ASD and 170 TD participants].

## Derivation of 20 RSNs

Scans were obtained using 3T MRI scanners at the five different sites. Acquisition parameters of the multiecho R-fMRI scan and structural scan as well as the preprocessing procedure are detailed in section 1 of the Supplement. All analyses described below were conducted in Montreal Neurological Institute 152 standard space.

To investigate functional connectivity alterations, we first extracted 20 spatially independent components by applying ICA (with dimensionality 20) as implemented in FSL MELODIC (27) to R-fMRI data of 75 TD participants. This TD sample included participants from each site and consisted of 25 children (6.9–11 years), 25 adolescents (12–17 years), and 25 adults (18–30 years) to obtain resting-state components representative for all sites and the full age range of our sample. The dimensionality was set to 20 to enforce a split of the sensory and motor systems into their primary and secondary components [as shown before by Smith *et al.* (32)], which enables a more detailed investigation of these systems. Visual inspection showed that the obtained components did not contain components representing noise, but instead all represented well-known and reproducible RSNs. This is likely related to the application of careful ICA-based correction for head motion effects [using ICA-AROMA [ICA-based Automatic Removal of Motion Artifacts] (33)] in our preprocessing pipeline. Accordingly, all 20 components were selected for further analyses. Figure 1 shows the spatial configuration of all RSNs, including sensory, motor, default mode, and task-related networks. The TD subjects used for the derivation of these RSNs were excluded from further analyses. For each of the remaining 138 TD and 265 ASD participants, we applied dual regression as implemented in FSL (34,35) to obtain the subject-specific spatial maps and mean time series (across all voxels in the spatial map) corresponding to the 20 RSNs.

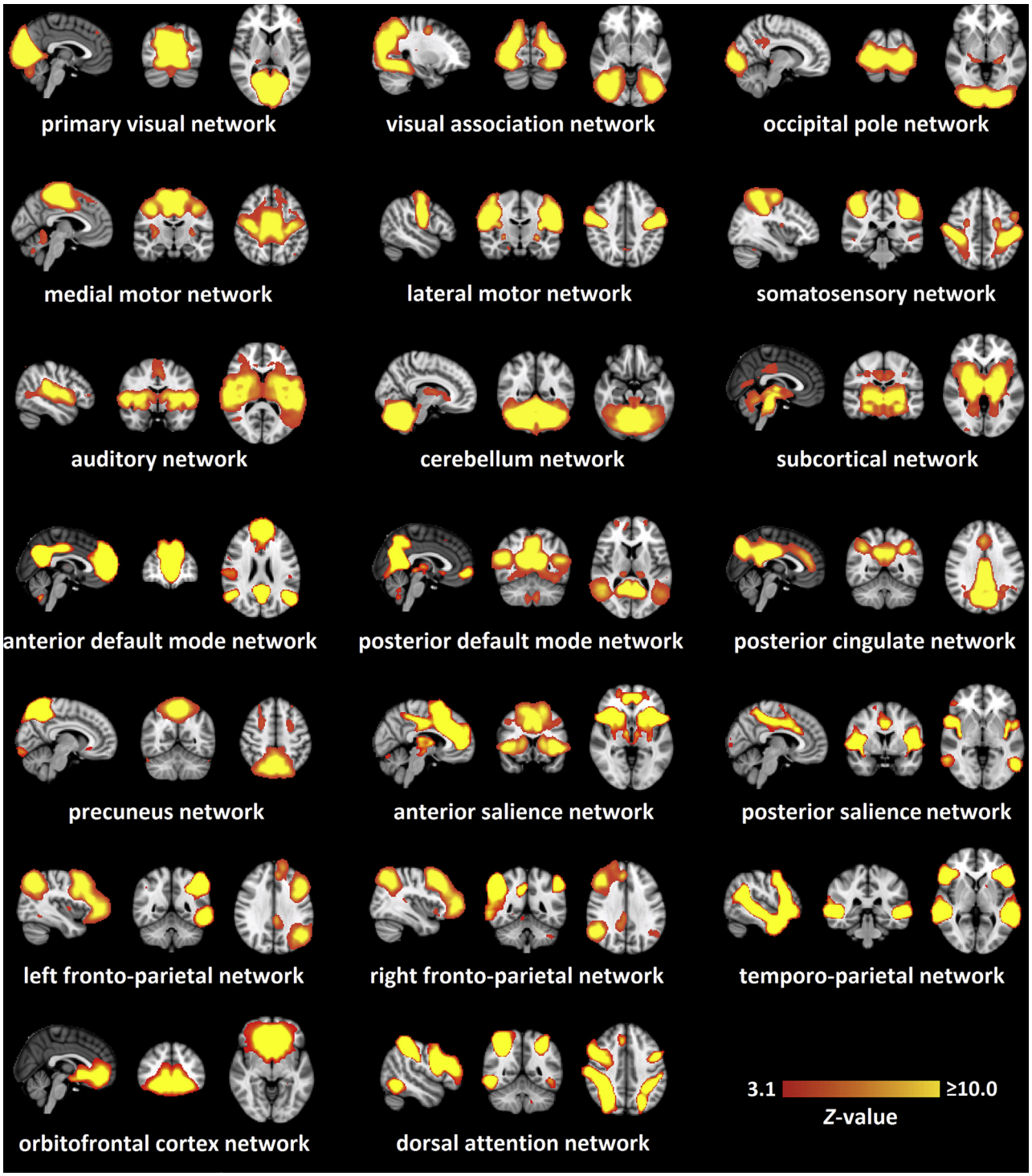


**Figure 1.** The 20 resting-state networks obtained using independent component analysis. All resting-state networks were used for further analyses. *Z*-stat maps are thresholded at $z > 3.1$ and shown in radiological convention.

## Investigation of Within-Network Connectivity

To examine alterations in within-network connectivity in ASD, we compared the spatial maps of the 20 RSNs between the TD group ($n$ = 138) and ASD group ($n$ = 265) using a categorical analysis. We also investigated how within-network connectivity changed as a function of autism traits, by examining the relationship between the spatial maps of the 20 RSNs and SRS-2 scores across all ASD and TD participants with SRS-2

scores available ($n$ = 358) in a continuous analysis. We conducted these analyses within the general linear modeling framework where we included, next to diagnostic group (categorical analysis) or the SRS-2 score (continuous analysis), nuisance variables for scan site, gender, and age. In both analyses, we applied permutation testing (with $n$ = 10,000 permutations) as implemented in FSL Randomise (36) to assess statistical significance. We further applied threshold-free cluster enhancement and familywise error correction. We corrected for testing multiple RSNs using a Bonferroni-corrected $p$ value of $p < .0025$ (i.e., .05/20 RSNs). For the statistical sensitivity of these analyses, refer to section 2 of the Supplement. Please note that we test influences of diagnosis and autism trait scores in separate statistical models, given that autism traits are an essential part of the diagnostics of ASD; in other words, those participants with very high autism trait scores by definition get an ASD diagnosis. Including them in one model would remove all variance shared between an ASD diagnosis and autism traits and thus would remove a large part of the variance associated with ASD.

### Investigation of Between-Network Connectivity

To investigate between-network connectivity, we computed Pearson and partial correlations between mean time series of the 20 RSNs obtained for every participant. For both correlation types, this resulted in 190 functional connections (i.e., between-network correlations). As opposed to Pearson correlations, partial correlations represent the association between two networks after accounting for the variance they share with all other networks in the analysis and can thus be interpreted as a measure of direct connectivity between networks. All of the following steps were conducted for both Pearson and partial correlations. The obtained correlations were transformed into normally distributed values using Fisher's $r$-to-$z$ transformation for every participant. We then applied an ordinary least squares regression for each correlation to correct for potential confounding effects of scan site, gender, and age. Next, we conducted a categorical analysis comparing between-network connectivity between the ASD and TD groups. More specifically, we tested group differences in the residual correlation strength for significance by means of permutation testing (with $n$ = 10,000 permutations) for every network pair. The $p$ values were obtained by calculating the fraction of permutated samples that yielded a group difference larger than the observed difference. In addition, we conducted a continuous analysis in which we investigated the relationship of between-network connectivity with SRS-2 scores across all participants. The $p$ values were obtained by calculating the fraction of permutated samples that yielded a correlation of SRS-2 scores with between-network connectivity higher than the observed correlation. In both the categorical and continuous analyses, we corrected for multiple comparisons by applying a false discovery rate correction ($q < 0.05$).

### Post Hoc Analyses

First, we conducted the continuous SRS-2 analyses in the ASD and TD groups separately to ensure that observed associations across all participants did not simply reflect a mean group difference in connectivity. In addition, we repeated all our analyses in children, adolescents, and adults separately to investigate whether additional connectivity alterations were revealed by investigating each age group independently, in light of potential developmental effects. We also checked whether the significant connectivity alterations identified in our analyses were specific to a particular ASD symptom domain. To this end, we examined post hoc correlations with the Short Sensory Profile (37), and with the Social Communication and Interaction and Restrictive Interests and Repetitive Behavior subscales of the SRS-2. Finally, we conducted sensitivity analyses to rule out that significant connectivity alterations were accounted for by head motion, informant (parent- or self-report SRS-2 score for the continuous analyses), gender, scan site, IQ, medication use, or comorbidity with attention-deficit/hyperactivity disorder. All post hoc analyses are detailed in section 7 of the Supplement.

## RESULTS

### Autism Trait–Related Aterations in Within-Network Connectivity

Comparing the spatial maps of the 20 RSNs between the ASD and TD groups did not reveal a main effect of diagnosis on functional connectivity within any of the 20 RSNs. However, the analysis in which we investigated continuous effects of autism traits by relating functional connectivity within the 20 RSNs to SRS-2 scores across all participants revealed significant associations for three networks (Figure 2). More specifically, we observed that functional connectivity increased with higher SRS-2 scores (i.e., more severe autism traits) within the anterior salience network (cluster in superior frontal gyrus), medial motor network (large cluster extending to superior frontal gyrus), and orbitofrontal cortex (OFC) network. These autism trait–related connectivity alterations were also significant when only investigating the ASD group—ensuring that these are not artificial correlations induced by a general difference in the mean of the ASD and TD groups (Supplemental Table S1, Supplemental Figure S1)—and correlated with atypical sensory processing, repetitive behaviors, and social impairments (Supplemental Table S2). Post hoc analyses further showed these connectivity alterations were not related to head motion, IQ, gender, scan site, age, medication use, comorbidities, or SRS-2 informant.

### Case-Control and Autism Trait–Related Alterations in Between-Network Connectivity

Next, we investigated ASD-related alterations in functional connectivity between the 20 RSNs. As shown in Table 2 and Figure 3, the categorical analysis revealed that Pearson correlations of 16 edges (i.e., functional connections between networks) differed significantly between the ASD and TD groups. Notably, 10 of the 16 significant edges included the visual association network or cerebellar network. Compared with the TD group, functional connectivity was decreased in the ASD group among the visual association, somatosensory, medial motor, and lateral motor networks. At the same time, functional connectivity of the cerebellum with all these sensory and motor networks was increased in ASD. Furthermore, post hoc analyses showed that connectivity for several of these

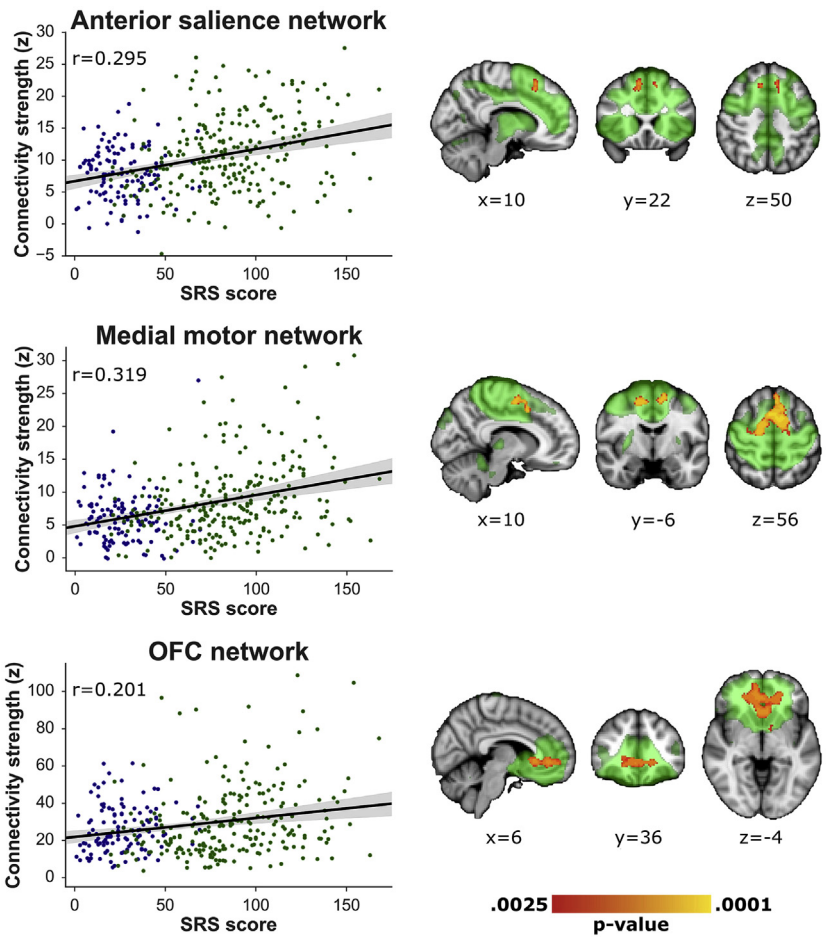


**Figure 2.** Significant autism trait–related alterations in within-network connectivity. Increased Social Responsiveness Scale Second Edition (SRS-2) scores were associated with increased functional connectivity within three resting-state networks. Left panels depict the continuous relationships between SRS-2 scores and connectivity strength within each of the significant clusters. Connectivity strength represents the mean *z*-stat value within the significant cluster for every subject. These *z*-stat values were derived from the subject-specific spatial maps generated by the dual regression approach (i.e., the general linear model parameter estimate statistical image normalized by the residual within-subject noise) corresponding to the independent component analysis–template networks. Data points from typically developing individuals are indicated in blue and data points from autism spectrum disorder individuals in green. Right panels show the significant clusters (red-yellow) overlaid on the respective resting-state networks (green; radiological convention). OFC, orbitofrontal cortex.

edges was associated with atypical sensory processing, repetitive behaviors, and/or social impairments (Supplemental Table S3). We observed no significant group differences in the partial correlation analyses.

In the continuous SRS-2 analysis, we observed significant associations for four network pairs: at higher SRS-2 scores, connectivity (i.e., Pearson correlations) of the cerebellum with the somatosensory and medial motor network increased, whereas connectivity of the OFC with the lateral motor network and posterior DMN decreased (Table 2, Figure 3). Marginally significant correlations with the SRS-2 ($r > \pm.15$, $p < .05$) (see Figure 3) were present for the visual association edges implicated in the categorical analysis; however, these did not survive false discovery rate correction. Also, the partial correlation analyses did not show significant between-network alterations.

Post hoc analyses confirmed that none of the significant categorical or continuous ASD-related alterations in between-network connectivity were accounted for by head motion, IQ, gender, scan site, medication use, or comorbidities, although some of the between-network connectivity differences were smaller or not yet present in childhood, warranting further investigation into the development of between-network connectivity in ASD (see Supplemental Table S5).

## DISCUSSION

We conducted a comprehensive investigation of ASD-related differences in within- and between-network functional connectivity in the large and clinically well-characterized EU-AIMS LEAP cohort. The key findings of our study are the differences observed in between-network connectivity: while connectivity between visual association, somatosensory, and motor networks was decreased, connectivity of the cerebellum with all these sensory and motor networks was increased in the ASD compared with the TD group. Furthermore, we observed that at higher autism trait severity, connectivity increased within the anterior salience, medial motor, and OFC networks. However, we did not replicate previously reported case-control differences in within-network connectivity.

### Impaired Multisensory and Visual-Motor Integration in ASD

We propose that the decreased functional connectivity among visual association, somatosensory, and motor networks underpins the abnormalities in multisensory and visual-motor integration observed in individuals with ASD. Over the last decade, a growing literature has reported atypical sensory processing in ASD, such as hypo- or hyperreactivity to sensory

**Table 2. Summary of Statistical Parameters of Significant Categorical and Continuous ASD-Related Alterations in Between-Network Connectivity**

| Network 1 | Network 2 | Mean Correlation (*z*) TD | Mean Correlation (*z*) ASD | Permuted *p* Value | FDR-Corrected *p* Value | Effect Size Cohen's *d* |
|---|---|---|---|---|---|---|
| Connectivity Decrease in ASD Group | | | | | | |
| Visual association | Somatosensory | 3.9502 | 2.5368 | .0030 | .0475 | −0.3116 |
| Visual association | Motor medial | 1.7351 | 0.3029 | .0002 | .0228 | −0.3819 |
| Visual association | Motor lateral | 2.7085 | 1.1762 | .0006 | .0228 | −0.3801 |
| Motor lateral | Motor medial | 7.4314 | 5.9793 | .0025 | .0432 | −0.3215 |
| Motor lateral | Somatosensory | 4.5549 | 4.1193 | .0034 | .0475 | −0.3022 |
| Cerebellum | Subcortical | 1.7674 | 0.2160 | .0011 | .0317 | −0.3520 |
| OFC | Motor lateral | −0.4978 | −1.5683 | .0015 | .0317 | −0.3470 |
| Connectivity Increase in ASD Group | | | | | | |
| Cerebellum | Somatosensory | −0.1909 | 0.9704 | .0006 | .0228 | 0.3526 |
| Cerebellum | Motor medial | −1.2208 | 0.0073 | .0014 | .0317 | 0.3417 |
| Cerebellum | Motor lateral | −0.7624 | 0.3023 | .0005 | .0228 | 0.3480 |
| Cerebellum | Visual association | 1.0814 | 1.9481 | .0035 | .0475 | 0.3127 |
| Cerebellum | Auditory | −0.2932 | 0.5087 | .0042 | .0499 | 0.3005 |
| Cerebellum | Temporal-parietal | 0.3017 | 1.1020 | .0042 | .0499 | 0.2943 |
| Motor medial | Salience anterior | 0.2993 | 1.4783 | .0014 | .0317 | 0.3256 |
| DMN anterior | Occipital pole | −0.2438 | 0.8762 | .0005 | .0228 | 0.3659 |
| DMN posterior | PCC | 7.2185 | 8.2413 | .0024 | .0432 | 0.3313 |

| | | Correlation With SRS-2 | Permuted *p* Value | FDR-Corrected *p* Value | Effect Size Cohen's *d* |
|---|---|---|---|---|---|
| SRS-2–Related Connectivity Alteration | | | | | |
| OFC | Motor lateral | −0.229 | .0001 | .0190 | N/A |
| OFC | DMN posterior | −0.169 | .0008 | .0342 | N/A |
| Cerebellum | Somatosensory | 0.174 | .0003 | .0190 | N/A |
| Cerebellum | Motor medial | 0.186 | .0002 | .0190 | N/A |

Mean correlations of the TD and ASD groups represent group-average *z*-transformed Pearson's correlations.

ASD, autism spectrum disorder; DMN, default mode network; FDR, false discovery rate; N/A, not applicable; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; SRS-2, Social Responsiveness Scale-2; TD, typically developing.

stimuli, enhanced sensory discrimination, and impaired multisensory integration (38,39). Moreover, the DSM-5 now includes atypical sensory processing as a diagnostic criterion (2), acknowledging the significance of these alterations in ASD. Similarly, evidence is emerging for impaired visual-motor integration in ASD (40,41). For example, children with ASD favor proprioceptive over visual feedback when learning novel movements (42), have difficulty incorporating visual input into movement planning (40), and show decreased performance on visual-motor coordination tasks (43). Our findings nicely concord with degree centrality-based (a graph theory metric indicating the connectedness of voxels) analyses of the EU-AIMS LEAP cohort, showing reduced connectedness of sensory and motor areas in the brain (S. Holiga *et al.*, M.Sc., unpublished data, January 2018). We also replicate a previous R-fMRI report showing decreased connectivity between the visual association and lateral motor network in ASD (44). The multitude of functional visual-motor and visual-sensory connections affected in the ASD group, as well as their association with not one specific, but multiple ASD symptom domains observed in our analysis, suggests that impaired visual-motor and multisensory integration—while relatively underexamined—could play a very central role in ASD. Indeed, visual-motor and multisensory integration are crucial for developing imitation skills and important for learning motor, communication, and social skills (45,46). Impairments in these skills comprise the core symptoms of ASD. Accordingly, and in accordance with Nebel *et al.* (44) and Jones and Prior (47), we hypothesize that our findings reflect impaired visual-motor and multisensory integration and may represent fundamental abnormalities underpinning various symptoms in ASD.

The increased connectivity of the cerebellum with seven cortical networks in the ASD group can be interpreted within the larger framework of structural and functional cerebellar alterations that frequently have been reported in ASD [for reviews, see (48,49)]. It is striking that most of the networks with which the cerebellum exhibited increased connectivity in ASD are again the networks underlying sensory and motor processing. While it was initially considered a motor region, various studies have now established an important role for the cerebellum in multimodal integration (50–52), suggesting that also hyperconnectivity of cerebellum with sensory and motor networks might be associated with impaired multisensory and sensorymotor integration. Our findings are consistent with work from Cerliani *et al.* (13) showing increased functional connectivity between the crus region of the cerebellum and a network including dorsal motor and somatosensory cortices in ASD (though we did not replicate the increased corticostriatal-thalamic connectivity observed in their study) and with the increased cerebrocerebellar connectivity reported by Khan *et al.*

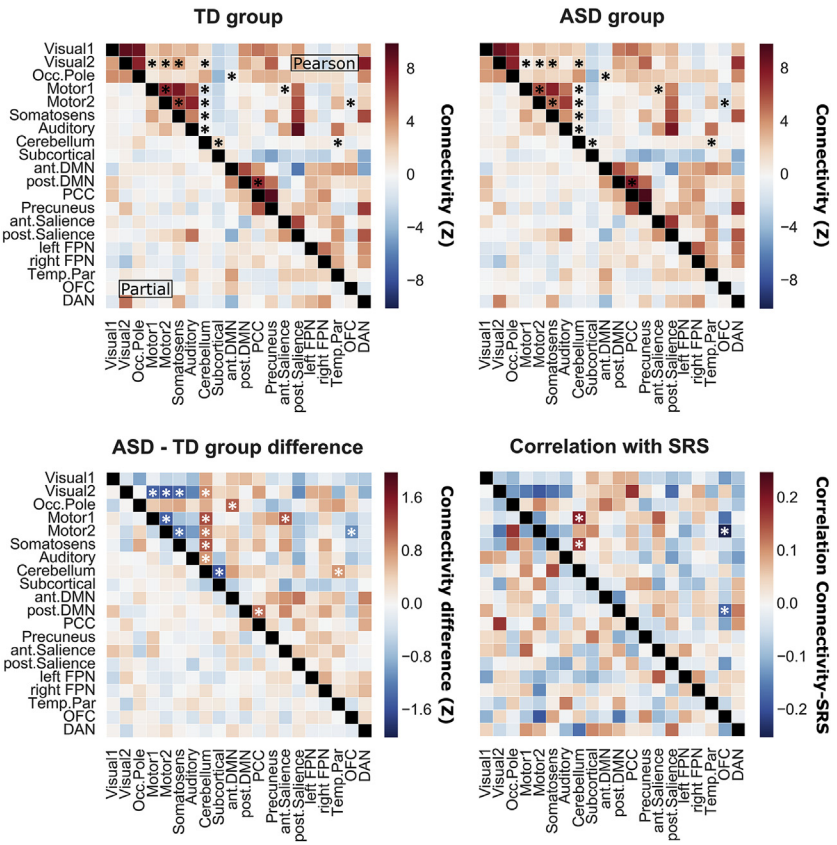


**Figure 3.** Between-network connectivity matrices. The top two matrices represent the group-average between-network connectivity matrices of the typically developing (TD) and autism spectrum disorder (ASD) groups. The bottom left matrix represents the difference in between-network connectivity between the ASD and TD groups, and the bottom right matrix shows the correlation of Social Responsiveness Scale Second Edition (SRS-2) scores with between-network connectivity (i.e., the correlation of SRS-2 scores with Pearson's or partial correlations between the time series of the 20 resting-state networks). *Z*-transformed Pearson's correlations are shown in the upper right triangle, and *z*-transformed partial correlations in the bottom left triangle of each matrix. Asterisks (*) indicate significant group differences (top and bottom left) or significant correlations with the SRS-2 score (bottom right); false discovery rate corrected, $q < 0.05$. The statistical parameters of these significant ASD-related alterations are listed in Table 2. ant.DMN, anterior default mode; ant.Salience, anterior salience; DAN, dorsal attention network; FPN, frontoparietal; Motor1, medial motor; Motor2, lateral motor; Occ.Pole, occipital pole; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; post.DMN, posterior default mode network; post.Salience, posterior salience; Somatosens, somatosensory; Temp.Par, temporoparietal; Visual1, primary visual; Visual2, visual association.

(53). Our findings are also in accordance with previously reported abnormalities in structural connectivity of cerebellar outputs (54). The increased functional connectivity of the cerebellum observed in our study might relate to the frequently reported reduction in gamma-aminobutyric acidergic Purkinje cells in ASD (55,56). These cerebellar neurons send inhibitory projections to the deep cerebellar nuclei, the output nuclei of the cerebellum. Loss of these neurons is thought to lead to disinhibition of the deep cerebellar nuclei (13,57), which could explain the observed shift from negative to positive (i.e., increased) cerebrocerebellar connectivity in the ASD group. While both decreased connectivity of the visual association network and increased connectivity of the cerebellum with sensory and motor networks strongly point to impaired multisensory and visual-motor integration in ASD, further research is necessary to determine how exactly these findings can be integrated.

## Autism Trait–Related Increases in Within-Network Connectivity

In our within-network analysis, we observed that at higher autism traits, functional connectivity increased within the anterior salience, medial motor, and OFC networks—across the sample as a whole and within the ASD group separately—and correlated with atypical sensory processing, repetitive behaviors, and social impairments. These networks correspond with networks implicated in previous case-control studies in ASD. For example increased connectivity within the salience network has been reported by R-fMRI studies before in ASD (14,58). The salience network is thought to be involved in selecting which of many internal and external stimuli one should pay attention to (59,60), and alterations in this network have been associated with hypersensitivity in ASD (21). Increased connectivity within the medial motor network has also been reported in ASD (14,61) and has been related to impairments in motor function in ASD (62). We further observed increased connectivity within the OFC network. Aberrant structure and function of the OFC has been observed in ASD before and has been related to social impairments in ASD (63–65). In contrast to previous reports (19,20), we did not observe altered connectivity in the DMN in this analysis, yet the between-network analysis revealed increased connectivity between two subnetworks of the DMN (the posterior DMN and posterior cingulate cortex network). It is further apparent that all symptom-related alterations observed in our analysis are increases in functional connectivity, whereas previous studies have also reported decreased within-network connectivity in ASD. In light of potential developmental effects, we checked for the influence of age on our findings. Post hoc analyses, however, showed that all ASD trait-related increases in connectivity were present across children, adolescents, and adults (Supplemental Table S4).

Although we demonstrated that connectivity within multiple networks was increased at higher SRS-2 scores in the

continuous analyses (which allow for larger individual variation), it is noteworthy that we did not replicate previously observed case-control differences in within-network connectivity [e.g., (9,11–14)]. A factor that might have contributed to the absence of significant categorical differences in within-network connectivity in our study is the heterogeneity in our large sample. The LEAP study specifically aimed to include a broad sample of individuals with ASD to provide a valid representation of the general (i.e., real-word) ASD population: participants across the entire autism spectrum were selected independent of gender and within a large age range. This approach might have concealed case-control differences in within-network connectivity detected in previous studies, which were mostly conducted in smaller and/or matched samples that were potentially more homogeneous. However, our sample likely reflects the actual heterogeneity present in ASD, while findings from previous studies using smaller, more homogeneous samples might not always generalize to the entire ASD population.

That being said, our significant findings should also be interpreted in the context of the large heterogeneity in ASD. As can be observed in Figure 2, intersubject variability is high and not all subjects with high ASD severity scores display high connectivity within the respective networks. Similarly, despite the significant case-control differences in between-network connectivity, effect sizes were small to medium (Table 2), and boxplots of these effects show substantial overlap between groups (Supplemental Figure S3). This indicates that while—on average—connectivity for these functional connections is altered in the ASD group, these alterations are not present in all individuals with ASD. This heterogeneity in ASD is often overlooked by the R-fMRI literature. Future work of the EU-AIMS LEAP consortium will focus on defining ASD subtypes based on the underlying connectivity profile (66) and normative modeling approaches (67), which will be key into further unraveling the potentially heterogeneous neurobiological mechanisms underlying ASD.

Finally, post hoc analyses did not reveal other significant ASD-related connectivity alterations when conducting our analyses in children, adolescents, and adults separately, in addition to the alterations that were already observed in our main analyses. However, some of the between-network (but not within-network) connectivity alterations in our main analyses were not present or were of smaller magnitude in children than in adolescents and adults. This implies potential effects of development affecting between-network connectivity. With the follow-up assessment of the LEAP cohort nearly completed, future work will include a longitudinal analysis to assess the precise effects of development on functional connectivity in ASD.

A limitation of our study is that while our findings strongly implicate impaired multisensory and visual-motor integration in ASD, the LEAP cognitive task battery did not include assessments of these domains, so future work will be necessary to confirm the direct link between aberrant between-network connectivity and impaired visual-motor and multisensory integration in ASD. Other limitations are that the continuous SRS-2 analysis was based on self-report scores for adult TD individuals compared with parent-report scores for all other participants, and that the ASD and TD groups significantly differed in the proportion of male and female participants, head motion, and IQ. However, sensitivity analyses revealed no influence of these factors on our findings.

## Conclusions

We demonstrate widespread alterations in functional connectivity between visual, cerebellum, and sensory-motor networks in ASD compared with control subjects, implicating a key role for impaired multisensory and visual-motor integration in ASD.

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## REFERENCES

1. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, *et al.* (2018): Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2014. MMWR Surveill Summ 67:1.
2. Association AP (2013): Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Washington, DC: American Psychiatric Pub.
3. Minshew NJ, Williams DL (2007): The new neurobiology of autism: Cortex, connectivity, and neuronal organization. Arch Neurol 64:945–950.
4. Just MA, Cherkassky VL, Keller TA, Minshew NJ (2004): Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. Brain 127:1811–1821.
5. Just MA, Keller TA, Malave VL, Kana RK, Varma S (2012): Autism as a neural systems disorder: A theory of frontal-posterior underconnectivity. Neurosci Biobehav Rev 36:1292–1313.
6. Hull JV, Jacokes ZJ, Torgerson CM, Irimia A, Van Horn JD (2017): Resting-state functional connectivity in autism spectrum disorders: A review. Front Psychiatry 7:205.
7. Picci G, Gotts SJ, Scherf KS (2016): A theoretical rut: Revisiting and critically evaluating the generalized under/over-connectivity hypothesis of autism. Dev Sci 19:524–549.
8. Rane P, Cochran D, Hodge SM, Haselgrove C, Kennedy DN, Frazier JA (2015): Connectivity in autism: A review of MRI connectivity studies. Harv Rev Psychiatry 23:223–244.
9. Ebisch SJ, Gallese V, Willems RM, Mantini D, Groen WB, Romani GL, *et al.* (2011): Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. Hum Brain Mapp 32:1013–1028.
10. Rudie JD, Hernandez LM, Brown JA, Beck-Pancer D, Colich NL, Gorrindo P, *et al.* (2012): Autism-associated promoter variant in MET impacts functional and structural brain networks. Neuron 75:904–915.
11. von dem Hagen EA, Stoyanova RS, Baron-Cohen S, Calder AJ (2012): Reduced functional connectivity within and between 'social' resting state networks in autism spectrum conditions. Soc Cogn Affect Neurosci 8:694–701.
12. Di Martino A, Kelly C, Grzadzinski R, Zuo XN, Mennes M, Mairena MA, *et al.* (2011): Aberrant striatal functional connectivity in children with autism. Biol Psychiatry 69:847–856.
13. Cerliani L, Mennes M, Thomas RM, Di Martino A, Thioux M, Keysers C (2015): Increased functional connectivity between subcortical and cortical resting-state networks in autism spectrum disorder. JAMA Psychiatry 72:767–777.
14. Uddin LQ, Supekar K, Lynch CJ, Khouzam A, Phillips J, Feinstein C, *et al.* (2013): Salience network–based classification and prediction of symptom severity in children with autism. JAMA Psychiatry 70:869–879.
15. Uddin LQ, Supekar K, Menon V (2013): Reconceptualizing functional brain connectivity in autism from a developmental perspective. Front Hum Neurosci 7:458.
16. Yerys BE, Herrington JD, Satterthwaite TD, Guy L, Schultz RT, Bassett DS (2017): Globally weaker and topologically different: Resting-state connectivity in youth with autism. Mol Autism 8:39.
17. Xu J, Wang H, Zhang L, Xu Z, Li T, Zhou Z, *et al.* (2018): Both hypo-connectivity and hyper-connectivity of the insular subregions associated with severity in children with autism spectrum disorders. Front Neurosci 12:234.
18. Hahamy A, Behrmann M, Malach R (2015): The idiosyncratic brain: distortion of spontaneous connectivity patterns in autism spectrum disorder. Nat Neurosci 18:302–309.
19. Doyle-Thomas KA, Lee W, Foster NE, Tryfon A, Ouimet T, Hyde KL, *et al.* (2015): Atypical functional brain connectivity during rest in autism spectrum disorders. Ann Neurol 77:866–876.
20. Assaf M, Jagannathan K, Calhoun VD, Miller L, Stevens MC, Sahl R, *et al.* (2010): Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients. Neuroimage 53:247–256.
21. Green SA, Hernandez L, Bookheimer SY, Dapretto M (2016): Salience network connectivity in autism is related to brain and behavioral markers of sensory overresponsivity. J Am Acad Child Adolesc Psychiatry 55:618–626.e61.
22. Nomi JS, Uddin LQ (2015): Developmental changes in large-scale network connectivity in autism. Neuroimage Clin 7:732–741.
23. Bassett DS, Yang M, Wymbs NF, Grafton ST (2015): Learning-induced autonomy of sensorimotor systems. Nat Neurosci 18:744.
24. Barber AD, Caffo BS, Pekar JJ, Mostofsky SH (2013): Developmental changes in within- and between-network connectivity between late childhood and adulthood. Neuropsychologia 51:156–167.
25. Charman T, Loth E, Tillmann J, Crawley D, Wooldridge C, Goyard D, *et al.* (2017): The EU-AIMS Longitudinal European Autism Project (LEAP): Clinical characterisation. Mol Autism 8:27.
26. Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005): Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360:1001–1013.
27. Loth E, Charman T, Mason L, Tillmann J, Jones EJH, Wooldridge C, *et al.* (2018): The EU-AIMS Longitudinal European Autism Project (LEAP): Design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders. Mol Autism Jun 23;8:24.
28. Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825–841.
29. Rutter M, Le Couteur A, Lord C (2003): Autism Diagnostic Interview—Revised. Los Angeles: Western Psychological Services. 29–30.
30. Lord C, Petkova E, Hus V, Gan W, Lu F, Martin DM, *et al.* (2012): A multisite study of the clinical diagnosis of different autism spectrum disorders. Arch Gen Psychiatry 69:306–313.
31. Constantino J, Gruber C (2012): Social Responsiveness Scale (SRS-2). Torrance, CA: Western Psychological Services.

32. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, *et al.* (2009): Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 106:13040–13045.
33. Pruim RH, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF (2015): ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112:267–277.
34. Beckmann CF, Mackay CE, Filippini N, Smith SM (2009): Group comparison of resting-state FMRI data using multi-subject ICA and dual regression. Neuroimage 47:S148.
35. Nickerson LD, Smith SM, Öngür D, Beckmann CF (2017): Using dual regression to investigate network shape and amplitude in functional connectivity analyses. Front Neurosci 11:115.
36. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014): Permutation inference for the general linear model. Neuroimage 92:381–397.
37. Dunn W (1999): Sensory profile: User's manual. San Antonio, TX: Psychological Corporation.
38. Marco EJ, Hinkley LB, Hill SS, Nagarajan SS (2011): Sensory processing in autism: A review of neurophysiologic findings. Pediatr Res 69:48R–54R.
39. Ben-Sasson A, Hen L, Fluss R, Cermak SA, Engel-Yeger B, Gal E (2009): A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. J Autism Dev Disord 39: 1–11.
40. Dowd AM, McGinley JL, Taffe JR, Rinehart NJ (2012): Do planning and visual integration difficulties underpin motor dysfunction in autism? A kinematic study of young children with autism. J Autism Dev Disord 42:1539–1548.
41. Glazebrook C, Gonzalez D, Hansen S, Elliott D (2009): The role of vision for online control of manual aiming movements in persons with autism spectrum disorders. Autism 13:411–433.
42. Marko MK, Crocetti D, Hulst T, Donchin O, Shadmehr R, Mostofsky SH (2015): Behavioural and neural basis of anomalous motor learning in children with autism. Brain 138:784–797.
43. Crippa A, Forti S, Perego P, Molteni M (2013): Eye-hand coordination in children with high functioning autism and Asperger's disorder using a gap-overlap paradigm. J Autism Dev Disord 43:841–850.
44. Nebel MB, Eloyan A, Nettles CA, Sweeney KL, Ament K, Ward RE, *et al.* (2016): Intrinsic visual-motor synchrony correlates with social deficits in autism. Biol Psychiatry 79:633–641.
45. Williams JHG, Whiten A, Singh T (2004): A systematic review of action imitation in autistic spectrum disorder. J Autism Dev Disord 34: 285–299.
46. Edwards LA (2014): A meta-analysis of imitation abilities in individuals with autism spectrum disorders. Autism Res 7:363–380.
47. Jones V, Prior M (1985): Motor imitation abilities and neurological signs in autistic children. J Autism Dev Disord 15:37–46.
48. Wang SS-H, Kloth AD, Badura A (2014): The cerebellum, sensitive periods, and autism. Neuron 83:518–532.
49. Becker EB, Stoodley CJ (2013): Autism spectrum disorder and the cerebellum. Int Rev Neurobiol 113:1–34.
50. Ishikawa T, Shimuta M, Häusser M (2015): Multimodal sensory integration in single cerebellar granule cells in vivo. Elife 4:e12916.
51. Ronconi L, Casartelli L, Carna S, Molteni M, Arrigoni F, Borgatti R (2016): When one is enough: Impaired multisensory integration in cerebellar agenesis. Cereb Cortex 27:2041–2051.
52. Xiao L, Scheiffele P (2018): Local and long-range circuit elements for cerebellar function. Curr Opin Neurobiol 48:146–152.
53. Khan AJ, Nair A, Keown CL, Datko MC, Lincoln AJ, Müller R-A (2015): Cerebro-cerebellar resting-state functional connectivity in children and adolescents with autism spectrum disorder. Biol Psychiatry 78:625–634.
54. Catani M, Jones DK, Daly E, Embiricos N, Deeley Q, Pugliese L, *et al.* (2008): Altered cerebellar feedback projections in Asperger syndrome. Neuroimage 41:1184–1191.
55. Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, *et al.* (1998): A clinicopathological study of autism. Brain 121:889–905.
56. Rubenstein J, Merzenich MM (2003): Model of autism: Increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2:255–267.
57. Belmonte MK, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ (2004): Autism and abnormal development of brain connectivity. J Neurosci 24:9228–9231.
58. Neufeld J, Kuja-Halkola R, Mevel K, Cauvet É, Fransson P, Bölte S (2018): Alterations in resting state connectivity along the autism trait continuum: A twin study. Mol Psychiatry 23:1659–1665.
59. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.
60. Menon V, Uddin LQ (2010): Saliency, switching, attention and control: A network model of insula function. Brain Struct Funct 214:655–667.
61. Washington SD, Gordon EM, Brar J, Warburton S, Sawyer AT, Wolfe A, *et al.* (2014): Dysmaturation of the default mode network in autism. Hum Brain Mapp 35:1284–1296.
62. Floris DL, Barber AD, Nebel MB, Martinelli M, Lai M-C, Crocetti D, *et al.* (2016): Atypical lateralization of motor circuit functional connectivity in children with autism is associated with motor deficits. Mol Autism 7:35.
63. Sato W, Kochiyama T, Uono S, Yoshimura S, Kubota Y, Sawada R, *et al.* (2017): Reduced gray matter volume in the social brain network in adults with autism spectrum disorder. Front Hum Neurosci 11:395.
64. Eack SM, Wojtalik JA, Keshavan MS, Minshew NJ (2017): Social-cognitive brain function and connectivity during visual perspective-taking in autism and schizophrenia. Schizophr Res 183:102–109.
65. Girgis RR, Minshew NJ, Melhem NM, Nutche JJ, Keshavan MS, Hardan AY (2007): Volumetric alterations of the orbitofrontal cortex in autism. Prog Neuropsychopharmacol Biol Psychiatry 31:41–45.
66. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, *et al.* (2017): Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 23:28.
67. Marquand AF, Rezek I, Buitelaar J, Beckmann CF (2016): Understanding heterogeneity in clinical cohorts using normative models: Beyond case-control studies. Biol Psychiatry 80:552–561.
68. Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97–113.
69. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R (2016): ADHD Rating Scale—5 for Children and Adolescents: Checklists, Norms, and Clinical Interpretation. New York: Guilford Publications.