Biological Psychiatry: CNNI

Archival Report

Atypical Brain Asymmetry in Autism—A Candidate for Clinically Meaningful Stratification

Dorothea L. Floris, Thomas Wolfers, Mariam Zabihi, Nathalie E. Holz, Marcel P. Zwiers, Tony Charman, Julian Tillmann, Christine Ecker, Flavio Dell'Acqua, Tobias Banaschewski, Carolin Moessnang, Simon Baron-Cohen, Rosemary Holt, Sarah Durston, Eva Loth, Declan G.M. Murphy, Andre Marquand, Jan K. Buitelaar, Christian F. Beckmann, and the EU-AIMS Longitudinal European Autism Project Group

ABSTRACT

BACKGROUND: Autism spectrum disorder ("autism") is a highly heterogeneous neurodevelopmental condition with few effective treatments for core and associated features. To make progress we need to both identify and validate neural markers that help to parse heterogeneity to tailor therapies to specific neurobiological profiles. Atypical hemispheric lateralization is a stable feature across studies in autism, but its potential as a neural stratification marker has not been widely examined.

METHODS: In order to dissect heterogeneity in lateralization in autism, we used the large EU-AIMS (European Autism Interventions—A Multicentre Study for Developing New Medications) Longitudinal European Autism Project dataset comprising 352 individuals with autism and 233 neurotypical control subjects as well as a replication dataset from ABIDE (Autism Brain Imaging Data Exchange) (513 individuals with autism, 691 neurotypical subjects) using a promising approach that moves beyond mean group comparisons. We derived gray matter voxelwise laterality values for each subject and modeled individual deviations from the normative pattern of brain laterality across age using normative modeling.

RESULTS: Individuals with autism had highly individualized patterns of both extreme right- and leftward deviations, particularly in language, motor, and visuospatial regions, associated with symptom severity. Language delay explained most variance in extreme rightward patterns, whereas core autism symptom severity explained most variance in extreme leftward patterns. Follow-up analyses showed that a stepwise pattern emerged, with individuals with autism with language delay showing more pronounced rightward deviations than individuals with autism without language delay.

CONCLUSIONS: Our analyses corroborate the need for novel (dimensional) approaches to delineate the heterogeneous neuroanatomy in autism and indicate that atypical lateralization may constitute a neurophenotype for clinically meaningful stratification in autism.

https://doi.org/10.1016/j.bpsc.2020.08.008

Autism spectrum disorder ("autism") is a neurodevelopmental condition characterized by social-communicative deficits, restricted and repetitive behaviors, and sensory abnormalities (1). One of the key characteristics of autism is its great phenotypical and biological heterogeneity (2,3). Particularly in the neuroimaging literature, results are mixed and inconsistent and have been attributed to this heterogeneity in the autism population. To provide a more coherent picture of the complex neuropathology of autism, it is critical to tackle its heterogeneity and identify the neural markers that are consistent across studies. Such markers can provide clinically relevant stratification of individuals with autism.

When it comes to identifying a consistently implicated neural feature in autism, a large body of literature converges toward a disruption of hemispheric specialization—one of the most fundamental biological properties of our brains (4,5). This basic organizational principle describes that the two hemispheres differ in their functional specialization and exhibit pronounced structural asymmetries (6,7). Functional specialization involves leftward lateralization of language and motor skills and rightward lateralization of spatial perceptual abilities (8). It is also evident in gray matter asymmetries, with the frontal opercular and temporal perisylvian regions and hippocampus exhibiting leftward asymmetries and the thalamus

SEE COMMENTARY ON PAGE 762

and posterior parietal cortex showing rightward asymmetries (9,10).

Individuals with autism exhibit impairments in left hemisphere skills such as social-communication, language, and motor-related symptoms, while appearing relatively intact in right hemisphere functions such as visuospatial skills (11). This lateralized pattern of deficits and strengths in autism has given rise to theories trying to reconcile its complex clinical profile with atypical structural hemispheric specialization (11). In the largest autism cohort to date, comprising more than 3000 subjects, individuals with autism presented with widespread leftward cortical reductions (12). Meta-analyses (13), reviews (14), and smaller studies (15–22) are in line with this, confirming either a reduction or even reversal of typical leftward asymmetries in language- and motor-related regions. However, even though atypical lateralization in autism is among the most replicated findings, results present with small to moderate effect sizes (12,13). This is mostly attributed to subtle effects being diluted by small underpowered samples and sample heterogeneity that can result from a range of codependent factors such as age, sex, handedness, different symptom profiles, and co-occurring conditions. For example, lateralization in neurotypical subjects becomes more pronounced through age-related maturational processes (23). This typical trajectory is disrupted in individuals with autism, showing increasing reversed rightward lateralization (24). Sex-related asymmetry differences are evident in that neurotypical males are usually more strongly lateralized while neurotypical females have a more symmetric distribution (25,26). How sex affects atypical asymmetry in autism is unknown. Handedness is one of the most strongly behaviorally associated features of brain asymmetry (27). Left-handed individuals have a higher chance of being bihemispherically or even right-lateralized compared with the 90% of right-handed individuals who are left-lateralized for language (28). Individuals with autism exhibit elevated rates of non–right-handedness, comprising both left- and mixed-handedness, which has been attributed to atypical specialization in the brain (16,29). It is thus likely that there are common underlying neural mechanisms influencing both. Associated co-occurring symptoms, such as early language delay (LD) or attention-deficit/hyperactivity disorder (ADHD), are also associated with atypical lateralization (14,17). For example, individuals with autism and early LD show more pronounced deviations from typical asymmetry than those without LD (17,30).

Delineating such heterogeneity remains one of the central tasks in autism research (31). However, there is still little effort to address this challenge methodologically. One promising novel approach in this regard is normative modeling (32,33). Similar to the use of growth charts in pediatric medicine, normative modeling aims to place each individual with respect to centiles of variation in the population and thereby facilitates a move away from classic case-control analyses that ignore individual differences. Applying normative modeling to cortical thickness estimates, Zabihi *et al.* (34) showed that individuals with autism exhibit highly individualized atypicalities of cortical development. Whether this applies to other features, such as laterality, remains to be established.

Here, to overcome small sample size, we leveraged the EU-AIMS (European Autism Interventions—A Multicentre Study for Developing New Medications) Longitudinal European Autism Project (LEAP) (35,36), which is the largest harmonized autism sample to date and is deeply phenotypically characterized. Previous studies in this sample reported altered resting-state intra- and internetwork connectivity (37–39), decreased density in structural gray matter covariations (40), and attenuated reward-processing responses (41), while at the same time reporting no task-related differences in the social brain network (42). The present study was designed to address heterogeneity in autism with regard to age, sex, handedness, and core and co-occurring symptoms in the context of brain lateralization, using novel individualized analyses: 1) we transcended classic case-control analysis and address interindividual variation by applying normative modeling (32,43), and 2) we aimed to identify laterality-related subtypes by considering co-occurring clinical symptoms in autism such as language development. Through capturing variation at the individual level in combination with addressing different sources of heterogeneity and using a consistent imaging feature in autism, our work provides a step toward precision neuroscience in autism.

METHODS AND MATERIALS

Participants

Participants were part of the EU-AIMS and AIMS-2-TRIALS LEAP (35,36) cohort—the largest European multicenter initiative aimed at identifying biomarkers in autism. Participants underwent comprehensive clinical, cognitive, and magnetic resonance imaging assessment at one of six collaborating sites (Figure S1). All participants with autism spectrum disorder had an existing clinical diagnosis of autism. For details on participants, study design, and exclusion criteria, see the Supplement and (36). The final sample comprised 352 individuals with autism (259 male and 93 female), and 233 neurotypical control subjects (154 male and 79 female) between 6 and 30 years. For details on demographic information, see Table 1.

Clinical and Cognitive Measures

IQ was assessed using the Wechsler Abbreviated Scales of Intelligence. The Autism Diagnostic Observation Schedule (44) measured clinical core symptoms of autism. The Autism Diagnostic Interview–Revised (ADI-R) (45) was used to measure parent-rated autistic symptoms and LD, which was defined as having onset of first words later than 24 months and/or first phrases later than 33 months. ADHD symptoms were assessed with the DSM-5 ADHD rating scale. Handedness was assessed with the short version of the Edinburgh Handedness Inventory (46). For further details on all cognitive measures, see the Supplement and (35).

Image Preprocessing

For magnetic resonance imaging data acquisition parameters, see the Supplement and Table S1. Structural T1-weighted images were preprocessed according to a validated laterality pipeline (17,47,48) using the CAT12 toolbox (http://www.

Table 1. Demographic and Clinical Characterization of the Longitudinal European Autism Project Sample

Characteristic	ASD Males (*n* = 259)	ASD Females (*n* = 93)	NT Males (*n* = 154)	NT Females (*n* = 79)	Post Hoc Analysis[a]
Age, Years	16.8 (5.4) [7.1–30.3]	16.9 (6.1) [6.8–30.3]	17.1 (5.9) [7.4–30.9]	16.4 (5.8) [6.9–28.5]	ns
Full Scale IQ	100 (18.9) [56–148]	97 (18.5) [57–131]	107 (15.1) [53–142]	107 (18.0) [52–142]	(ASD M = ASD F) < (NT M = NT F)
Verbal IQ	98 (18.8) [52–160]	97 (18.6) [50–136]	105 (16.3) [46–142]	107 (19.6) [51–160]	(ASD M = ASD F) < (NT M = NT F)
Performance IQ	101 (21.0) [44–150]	97 (19.7) [55–133]	108 (17.3) [51–147]	105 (18.4) [58–139]	(ASD M = ASD F) < (NT M = NT F)
ADI-R					
Social	17.2 (6.4) [1–28]	15.5 (7.1) [1–29]	–	–	ns
Communication	13.8 (5.7) [0–26]	12.4 (5.3) [0–24]	–	–	ASD M > ASD F
RRB	4.5 (2.7) [0–12]	3.8 (2.6) [0–10]	–	–	ASD M > ASD F
ADOS-2					
Social-Affect	6.2 (2.6) [1–10]	5.3 (2.5) [1–10]	–	–	ASD M > ASD F
RRB	4.9 (2.8) [1–10]	4.3 (2.6) [1–9]	–	–	ns
CSS total	5.6 (2.8) [1–10]	4.5 (2.5) [1–10]	–	–	ASD M > ASD F
Handedness[b]	176 (80.3%) R 34 (16.3%) L 7 (3.4%) A	71 (84.5%) R 9 (10.7%) L 4 (4.8%) A	105 (89.7%) R 9 (7.7%) L 3 (2.6%) A	56 (83.3%) R 8 (12.1%) L 2 (3%) A	(ASD M = ASD F) < (NT M = NT F)
ADHD	106 ADHD+ 109 ADHD−	34 ADHD+ 52 ADHD−	–	–	ns
LD	76 LD 100 NoLD	19 LD 47 NoLD	–	–	ns

Results are presented as mean (SD) [range], *n* (%), or *n*.

A, ambidextrous; ADHD, attention-deficit/hyperactivity disorder; ADI-R, Autism Diagnostic Interview—Revised; ADOS-2, Autism Diagnostic Observation Schedule, Second Edition; ASD, autism spectrum disorder; CSS, calibrated severity score based on ADOS-2; F, females; L, left-handed; LD, language delay; M, males; NoLD, no language delay; ns, nonsignificant; NT, neurotypical; R, right-handed; RRB, restricted and repetitive behavior.

[a]Post hoc analyses were computed using analysis of variance tests (or χ^2 tests in the case of categorical variables).

[b]Handedness was assessed with the short version of the Edinburgh Handedness Inventory. Scores ranged between +500 (right-handed) and −500 (left-handed). To characterize demographics here, a categorical variable was computed comprising right-handed (+150 to +500), ambidextrous (−149 to +149), and left-handed (−500 to −150).

neuro.uni-jena.de/cat/) (see Figure S2). All original images were segmented and affine registered to a symmetrical tissue probability map before being reflected across the cerebral midline (x = 0). All segmented reflected and original (non-reflected) gray matter maps were then used to generate a symmetrical study–specific template via a flexible high-dimensional nonlinear diffeomorphic registration algorithm (DARTEL) (49). They were next registered to the symmetrical study–specific template as per standard DARTEL procedures. An intensity modulation step was included to retain voxelwise information on local volume (48). The final resulting images were modulated, warped, reflected (I_{ref}), and nonreflected (I_{nref}) gray matter intensity images. A laterality index was calculated at each voxel using the following formula: $2(I_{nref} - I_{ref})/(I_{nref} + I_{ref})$. Positive values in the right hemisphere of the laterality image indicate rightward asymmetry, and negative values in the right hemisphere of the laterality image indicate leftward asymmetry. Laterality index values in the left hemisphere have identical magnitude but opposite sign and were therefore excluded from further analyses. Laterality images were smoothed with a 4-mm full width at half maximum isotropic Gaussian kernel.

Normative Modeling

The normative modeling method has been described in detail previously (32,34,50–52). In summary, we estimated a normative brain aging model at each gray matter laterality voxel by using Gaussian process regression (53), a Bayesian nonparametric interpolation method that yields coherent measures of predictive confidence in addition to point estimates (for details see the Supplement). With this method, we could predict both the expected regional gray matter asymmetry changes and the associated predictive uncertainty for each individual, allowing us to quantify the voxelwise deviation of gray matter asymmetry from the neurotypical range across the entire brain.

First, we trained a Gaussian process regression model at each voxel on the neurotypical cohort using age, sex, and site as covariates to predict gray matter asymmetry, resulting in a developmental model of gray matter asymmetry in neurotypical individuals. To avoid overfitting, assess generalizability, and determine whether neurotypical individuals fall within the normative range, we used 10-fold cross-validation in neurotypical individuals before retraining the model in the entire sample to make predictions in individuals with autism. We generated normative probability maps, which quantify the deviation of each participant from the normative model for gray matter asymmetry at each voxel. These subject-specific *Z* score images provide a statistical estimate of how much each individual's true laterality value differs from the predicted laterality value with reference to the neurotypical pattern at each voxel given the participant's age, sex, and site. Normative probability maps were thresholded at an absolute value of $|Z|$

$>$ 2.6 (32,51). Based on this fixed threshold, we defined extreme rightward-lateralized (positive) and extreme leftward-lateralized (negative) deviations for each participant.

The accuracy of the normative model was evaluated using the correlation between the true and the predicted voxel values generated under 10-fold cross-validation. The neurotypical correlation map was restricted to positive values (i.e., loci with a negative correlation between predicted and true value were excluded) and further analyses were conducted on normative model maps thresholded with this. We included an additional, stringent thresholding of this correlation map, using statistical tests (false discovery rate [FDR] correction) for all normative models, and recomputed all main effects on the basis of voxels significantly different from chance (see the Supplement). For unthresholded correlation maps along with root mean square error maps, see Figures S3 and S4.

All extreme deviations per subject were summarized into (log-transformed) scores representing the percentage of extreme rightward and extreme leftward deviations per subject in relation to the total number of intracerebral voxels. These percentage scores were compared by calculating a general linear model including diagnosis and sex as the regressors of interest and age as covariate. Effect sizes were computed using partial eta squared (η_p^2) for analyses of variance, Cohen's *d* for *t* tests, and Cohen's ω for χ^2 tests. To compare our normative modeling against a conventional group-mean difference analysis we ran Permutation Analysis of Linear Models (PALM) on the laterality images examining the sex-by-diagnosis(-by-age) interaction with site as covariate.

Spatial Characterization of Deviations

We applied two strategies to spatially characterize the extreme rightward and leftward deviations. First, we generated spatial overlap maps for individuals in the same diagnostic and sex group by summing up the number of extreme deviations in each voxel for each subject. These were then divided by the total number of subjects (multiplied by 100) to represent the percentage of extreme right- and leftward deviations per brain voxel. Second, we extracted extreme rightward and leftward deviations within structurally [Harvard-Oxford atlas (54)] and functionally [neurosynth (http://neurosynth.org, accessed June 2019) (55)] defined regions of interest (ROIs) (see the Supplement). For latter, we used the search terms "language," "motor" (left-lateralized), "visuospatial," "attention" (right-lateralized), "monitoring," and "mentalizing" (no lateral bias). All results from these ROI-based post hoc analyses were FDR corrected.

Relative Contributions of Different Cognitive and Behavioral Measures

We ran relative importance analyses within individuals with autism including variables related to lateralization such as LD, ADHD, handedness, sex, and Autism Diagnostic Observation Schedule 2 calibrated severity score (CSS). This was done in a sample with reduced sample size (n = 305) without missing values on these variables. We used averaging over orderings (56) to rank the relative contribution of highly correlated regressors to the linear regression model. The variable showing strongest contribution to explained variance was followed up with additional analyses.

Symptom Associations

An individual-level atypicality score was estimated for each individual through extreme value statistics by computing the 10% trimmed mean of the 1% top deviations (34). We then computed 1-tailed Pearson's correlations between these individual atypicality scores and the ADI-R and Autism Diagnostic Observation Schedule 2 symptom severity scores. All correlation results were FDR corrected.

Robustness and Replicability

To assess robustness, we conducted a set of control analyses. 1) We estimated a separate normative model without including site as a covariate, but removing site effects using ComBat (57). 2) Another separate normative model was run, including handedness as an additional regressor. 3) For the sake of comparability, we also applied FDR correction (58) to the normative probability maps as an alternative to thresholding at $|Z| > 2.6$. 4) To address confounders, we repeated second-level statistical analyses controlling for Full Scale IQ, handedness, and socioeconomic status in a separate model. 5) To test whether the effects were robust against the influence of intellectual disability, we reran analyses excluding individuals with Full Scale IQ $<$ 70. 6) To further test the influence of handedness, we reran second-level analyses in right-handed subjects only. 7) Finally, as individuals with autism with and without LD were not matched on certain demographic variables, we additionally created a subsample matched for age and symptom severity and reran second-level statistical analyses to assess robustness of results. To assess replicability, we selected a sample from the publicly available Autism Brain Imaging Data Exchange (ABIDE) I and II (59,60) to examine extreme right- and leftward deviations in an independent dataset. For details, see the Supplement and Table S2.

RESULTS

The classic PALM analysis to assess mean group differences did not yield any significant results. Figure 1 depicts the spatial representation of the voxelwise normative model in neurotypical males in the largest site (labeled KCL) (n = 42). Results were similar for neurotypical females (Figure S5) and when using ComBat to address site effects (Figure S6). As site was included in the normative model, there are separate distributions for each site by sex, which are shown in Figure S7. In both neurotypical males and females, leftward shifts in gray matter asymmetry were mainly evident in Heschl's gyrus, planum temporale, parietal and central operculum, angular gyrus, supramarginal gyrus, pars triangularis, postcentral gyrus, precentral gyrus, superior and middle frontal gyrus, lateral occipital cortex, and cerebellum. Rightward shifts in gray matter asymmetry mainly occurred in middle and inferior temporal gyrus, posterior supramarginal gyrus, angular gyrus, superior parietal lobule, precuneus, anterior cingulate cortex, supracalcarine cortex, lingual gyrus, occipital pole, and caudate.

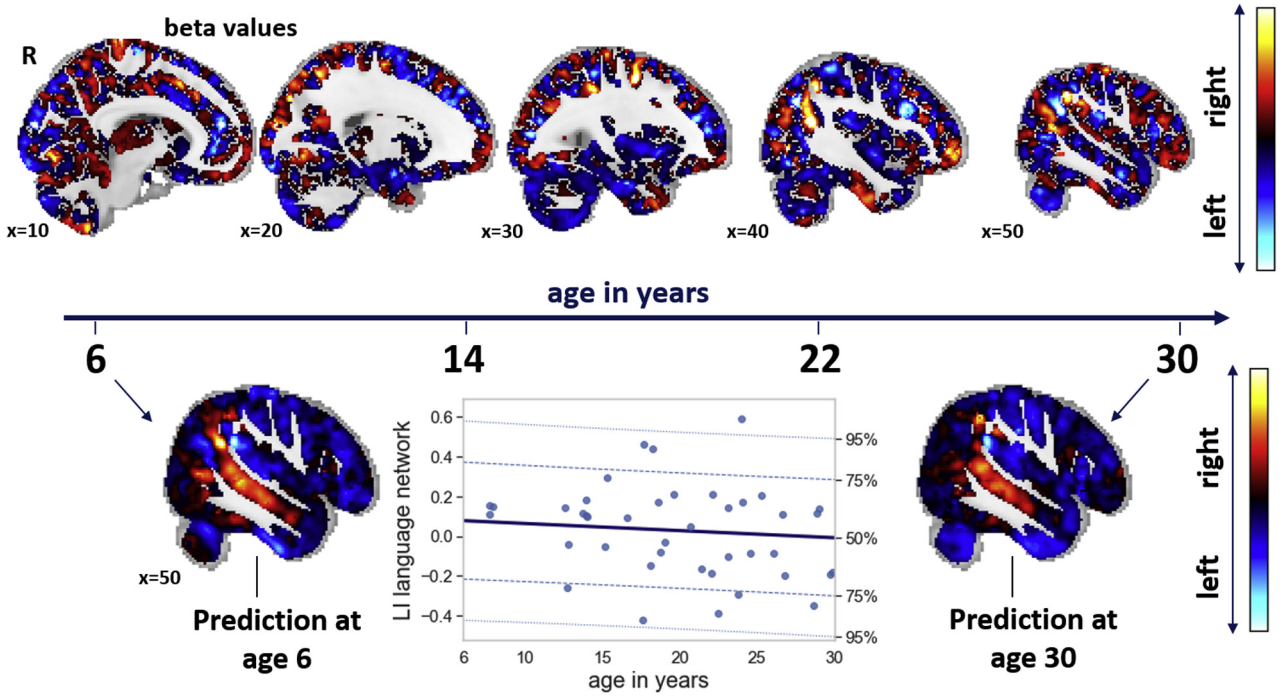

Figure 1. Normative developmental changes for gray matter laterality in neurotypical males. Spatial representation of the voxelwise normative model in neurotypical males from the KCL site. The upper panel shows the beta values of laterality change across 6 to 30 years of age. The lower panel shows the actual prediction of gray matter laterality at ages 6 and 30. Blue indicates a shift toward leftward asymmetry, and red indicates a shift toward rightward asymmetry. The regression line depicts the predicted laterality values extracted from the peak voxel of the language network based on neurosynth (x = 24, y = 54, z = 51) between 6 and 30 years of age along with centiles of confidence. These are based on the normative model maps thresholded with the positive correlation map between true and predicted values. Blue dots are the true values for neurotypical males from the KCL site. LI, laterality index; R, right.

Characterization of Extreme Deviations

Overall, males and females with autism showed significantly more extreme rightward ($F_{1,580}$ = 12.5, $p < .001$, η_p^2 = .021) and leftward ($F_{1,580}$ = 12.0, $p < .001$, η_p^2 = .02) deviations compared with neurotypical males and females (Figure 2). There were no significant sex differences (right: $F_{1,580}$ = 0.2, p = .67, $\eta_p^2 < .01$; left: $F_{1,580}$ = 0.2, p = .67, $\eta_p^2 < .01$) nor sex-by-diagnosis interactions (right: $F_{1,580}$ = 2.2, p = .14, $\eta_p^2 < .01$; left: $F_{1,580}$ = 0.5, p = .47, $\eta_p^2 < .01$). Controlling the FDR at the individual level of each normative probability maps led to identical conclusions (see the Supplement and Figure S8). Overall, individuals with autism showed no differences in the amount of extreme right- and leftward deviations (t_{702} = 0.04, p = .9). Furthermore, there was a significant positive correlation between extreme right- and leftward deviations (r = .41, $p < .001$). For rightward deviations, females with autism showed the highest overlap in parahippocampal gyrus, putamen, and amygdala, while males with autism showed the highest overlap mostly in the middle temporal gyrus and hippocampus (Figure 2A). For leftward deviations, females with autism showed highest overlap in orbitofrontal cortex, frontal pole, and postcentral gyrus, while males with autism showed the highest overlap mostly in lateral occipital cortex, temporal pole, and thalamus (Figure 2B). On average, females with autism had higher overlap of deviating regions than males with autism (right: χ^2 = 680, $p < .001$, $\omega < 0.01$; left: χ^2 = 282, $p < .001$, $\omega < 0.01$).

When considering deviations by structural ROIs, we found a significant main effect of diagnosis in the frontal operculum ($F_{1,580}$ = 15.7, $p < .001$, η_p^2 = .026) and central operculum ($F_{1,580}$ = 14.9, $p < .001$, η_p^2 = .025), with individuals with autism showing more extreme rightward deviations, and in the superior lateral occipital cortex ($F_{1,580}$ = 14.4, $p < .001$, η_p^2 = .024), with individuals with autism showing more extreme leftward deviations. Furthermore, there was a significant sex-by-diagnosis interaction in the temporal occipital fusiform cortex ($F_{1,580}$ = 19.2, $p < .001$, η_p^2 = .032), with females with autism having more extreme rightward deviations. When considering deviations by functional ROIs, individuals with autism showed extreme rightward deviations in the motor network ($F_{1,580}$ = 9.8, p = .001, η_p^2 = .017) and more extreme leftward deviations in the visuospatial network ($F_{1,580}$ = 11.6, $p < .001$, η_p^2 = .02). Results were robust across sensitivity analyses (see the Supplement).

Relative Contributions

Results revealed that LD had the relatively largest importance for explaining extreme rightward deviations (% of total R^2 [5.73%]: LD 65.7% > handedness 12.0% > ADHD 11.2% > sex 10.6% > CSS 0.5%), while symptom severity had the relatively largest importance for explaining extreme leftward deviations (% of total R^2 [4.56%]: CSS 37.7% > LD 32.2% > sex 13.0% > ADHD 9.7% > handedness 7.1%) (Figure 3). LD

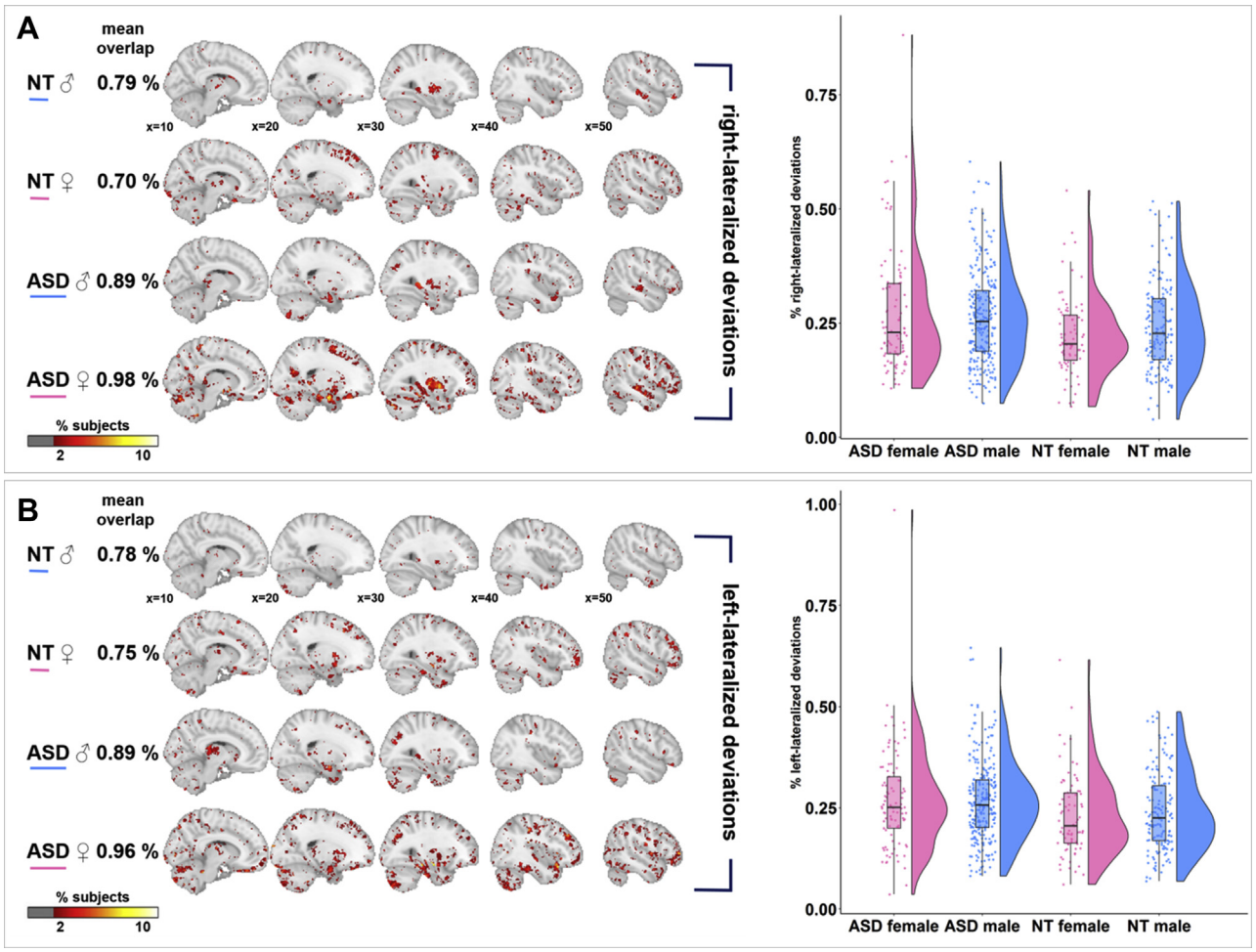

Figure 2. Characterization of extreme laterality deviations: **(A)** extreme rightward deviations and **(B)** extreme leftward deviations. The left panels show the percentage of extreme right-and leftward deviations from the normative model at each brain locus for each diagnostic group and sex separately. We depict loci where at least 2% of the subjects show overlaps. The violin plots on the right show the extreme deviations for each individual within each diagnostic and sex group. On average, individuals with autism show more extreme deviations than neurotypical control subjects for both right- and leftward deviations. ASD, autism spectrum disorder; NT, neurotypical.

was further followed up, showing a significant main effect for rightward deviations ($F_{2,468}$ = 10.5, $p < .001$, η_p^2 = .043). Specifically, individuals with autism and LD were different from both individuals with autism without LD (t_{213} = 2.5, p = .01, d = 0.32) and neurotypical individuals (t_{152} = 4.6, $p < .001$, d = 0.58), while individuals with autism without LD were not different from neurotypical individuals, though trending (t_{256} = 1.9, p = .06, d = 0.21). This stepwise pattern was overall more pronounced in males than in females with autism (Figure 4; Figure S9).

Results by language-related ROIs showed a main effect of LD for extreme rightward deviations in the frontal operculum ($F_{2,468}$ = 10.6, $p < .001$, η_p^2 = .043), central operculum ($F_{2,468}$ = 7.4, $p < .001$, η_p^2 = .03), and motor network ($F_{2,468}$ = 6.9, p = .001, η_p^2 = .029). Rightward deviations in the language network were significant ($F_{2,468}$ = 4.1, p = .01, η_p^2 = .017) but did not survive FDR correction. For all, there was a stepwise pattern, with individuals with autism and LD showing more pronounced deviations. For a characterization of the other variables see the Supplement, Figure S10, and Table S3.

Symptom Associations

Across the whole brain, there were significant associations between extreme rightward deviations and ADI-R communication scores (r = .14, p = .004). No correlations survived FDR correction in individuals with autism with and without LD. In males with autism, there were significant positive correlations between rightward deviations and core autism symptoms (ADI-R social: r = .18, p = .002; ADI-R communication: r = .19, p = .001). In females with autism, as well as in males and females with autism with and without LD, no results survived FDR correction.

Replicability

In line with the results of the EU-AIMS LEAP sample, males and females with autism of the combined ABIDE dataset

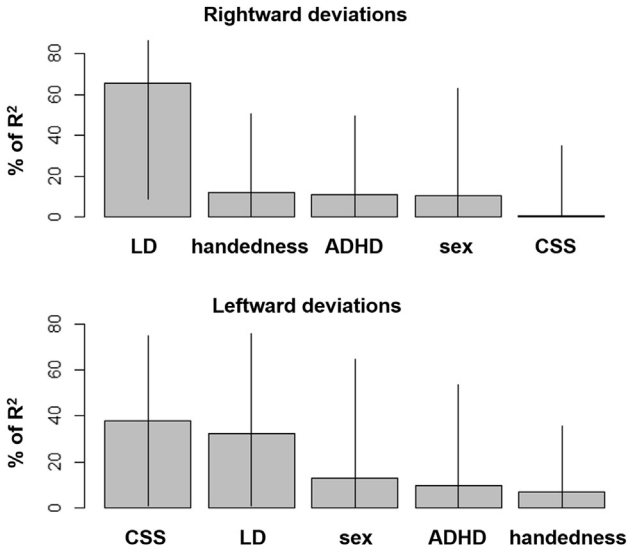

Figure 3. Relative importance of extreme laterality deviations. Language delay (LD) was defined as having onset of first words later than 24 months and/or having onset of first phrases later than 33 months. Attention-deficit/hyperactivity disorder (ADHD) symptoms were assessed with the DSM-5 ADHD rating scale, covering both inattention and hyperactivity/impulsivity symptoms. A categorical variable was computed based on the DSM-5 criteria. Symptom severity was captured by the total Autism Diagnostic Observation Schedule 2 calibrated severity score (CSS). We median-split the CSS measure into one group of individuals with autism with high CSS and one with low CSS. Based on the short version of Edinburgh Handedness Inventory, a categorical variable comprising right-handed (+500 to +150) and non–right-handed (−500 to +149) individuals was computed. Categorical variables were input in the model for LD, sex, ADHD, CSS, and handedness. Based on the R package "relaimpo" (https://cran.r-project.org/web/packages/relaimpo/), LD had the largest contribution to the total R^2 (5.73%) for extreme rightward deviations, whereas symptom severity had the largest contribution to the total R^2 (4.56%) for extreme leftward deviations. Bar plots are depicted with bootstrapped (n = 1000) confidence intervals of the relative importance metric for each factor.

showed both significantly more extreme rightward ($F_{1,1199}$ = 7.1, p = .008, η_p^2 = .01) and leftward ($F_{1,1199}$ = 11.6, $p < .001$, η_p^2 = .01) deviations compared with neurotypical individuals (see Figure S11). As in EU-AIMS LEAP, there were no sex differences (right: $F_{1,1199}$ = 0.3, p = .59, $\eta_p^2 < .01$; left: $F_{1,1199}$ = 0.04, p = .85, $\eta_p^2 < .01$) and no sex-by-diagnosis interactions (right: $F_{1,1199}$ = 3.6, p = .06, $\eta_p^2 < .01$; left: $F_{1,1199}$ = 3.4, p = .06, $\eta_p^2 < .01$). When considering deviations by functional ROIs significant in the primary analysis, individuals with autism also showed extreme rightward deviations in the motor network ($F_{1,1199}$ = 5.2, p = .02, η_p^2 = .004) and extreme leftward deviations in the visuospatial network ($F_{1,1199}$ = 4.0, p = .05, η_p^2 = .003). There were no significant group differences when considering the structural ROIs. For further details, see the Supplement and Figure S11.

DISCUSSION

In this study, we mapped extreme deviations in structural asymmetry at the individual level compared with a normative model of laterality development. A further aim was to explore laterality as a stratification marker in autism in a large and deeply phenotyped cohort and an equally large replication cohort. We found highly individualized patterns of both right- and leftward asymmetry deviations in males and females with autism. In contrast, when using classic case-control analyses, we did not detect any significant group differences, emphasizing the need to move beyond group averages to capture an accurate representation of the phenotype at the individual level. Similarly, a recent study addressing heterogeneity dimensionally pointed out that traditional case-control analyses yield smaller effects and miss atypicalities detected with a dimensional subtyping approach (61). By deriving statistical inferences at the individual level, we demonstrated that individuals with autism show a different, individualized pattern that would otherwise be missed when focusing on a common neurobiological signature. In fact, spatial overlap of extreme deviations across subjects (intersubject consistency) was minimal in both males and females with autism (Figure 2; Figure S11), corroborating the high degree of heterogeneity across subjects and the need to use methods that consider this large variation across subjects at the individual level.

Overall, we detected laterality deviations of small effect sizes, which is in line with previous reports in both autism (12) and the typical population (62). This further emphasizes the need for sufficiently powered large-scale datasets to unravel subtle patterns of atypical structural asymmetries. Moreover, extreme right- and leftward deviations were highly correlated with each other, which suggests that biological factors acting on atypical laterality shifts might not be biased toward one side in the same individual in autism. It thus also appears that a disruption in establishing the typical laterality pattern is not confined to one hemisphere, but that there are interrelated alterations in both. The biological underpinnings are unknown, but they likely include genetic (63), prenatal endocrine (64), and environmental factors. For instance, Geschwind and Behan (65) reported that left frontal regions (coinciding with frontal regions showing extreme rightward deviations in individuals with autism as described here) are under less genetic control than the right hemisphere and therefore are more susceptible to environmental influences during neurodevelopment. Whether prenatal androgens and related early immune activation (64,66) contribute to atypical hemispheric development in autism remains to be established.

Extreme rightward deviations were most pronounced in the motor network and frontal operculum and extreme leftward deviations in the visuospatial network. Accordingly, rightward shifts in asymmetry in language-related regions, particularly in Broca's area, are frequently reported in autism (18,19,67). However, atypical lateralization of motor and visuospatial performance is underexplored in autism. Accumulating evidence suggests the important role of motor-related asymmetries in the neurobiology of autism (5,15,68,69). Despite mostly intact visuospatial performance in autism, atypical activation patterns have been reported in individuals with autism while performing visuospatial tasks (70). More specific cognitive measures are needed to establish the functional relevance of these alterations.

Males and females with autism showed a similar degree of extreme deviations (Figure 2). Specifically, in the temporal occipital fusiform cortex, females with autism showed stronger rightward deviations, while both males with autism and neurotypical females show fewer rightward deviations than

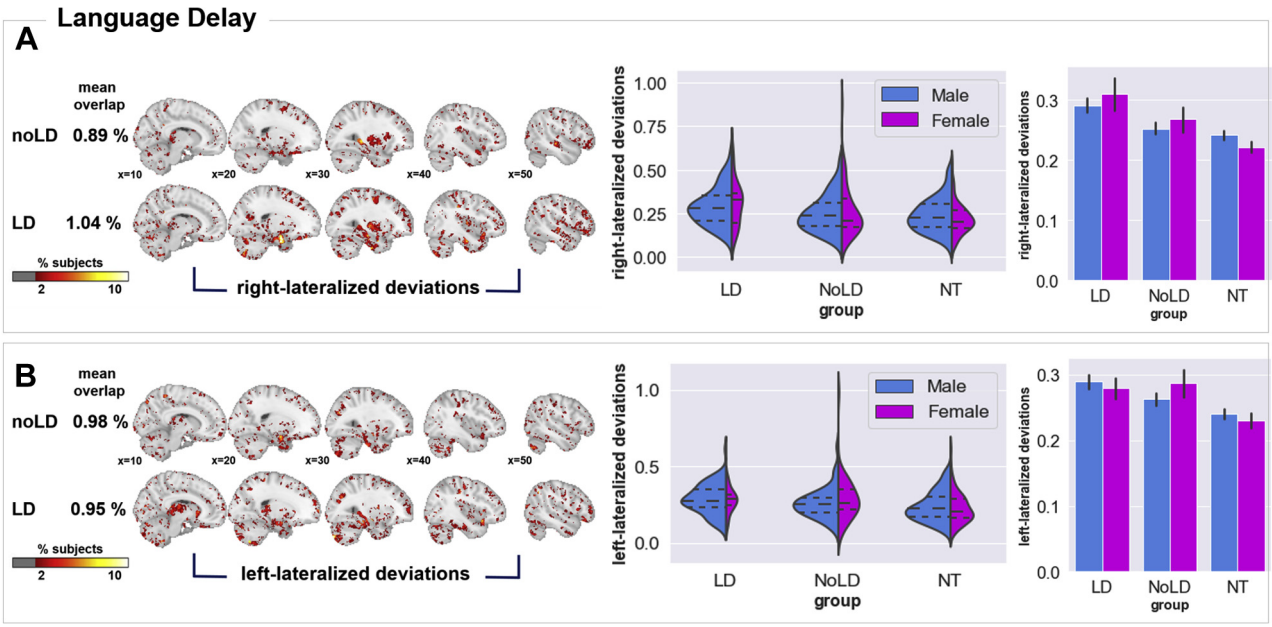

Figure 4. Extreme laterality deviations as a function of language delay (LD): **(A)** extreme rightward deviations and **(B)** extreme leftward deviations. Language delay was defined as having onset of first words later than 24 months and/or having onset of first phrases later than 33 months. The left panels show the percentage of extreme right- and leftward deviations from the normative model at each brain locus for each diagnostic group and sex separately. We depict loci where at least 2% of the subjects show overlaps. The violin and bar plots on the right show that individuals with autism with LD show more extreme rightward deviations than the other two groups. NoLD, individuals with autism without language delay; NT, neurotypical subjects.

neurotypical males. This "occipital face area" is strongly right-lateralized in neurotypical individuals (71). Individuals with autism exhibit atypical face-processing strategies, and these are more pronounced in females with autism (72). Being one of the most reported impairments in social cognition in autism, face processing and related atypical, sex-differential lateralization await further exploration.

When considering the spatial extent of deviations, females with autism show on average greater overlap across differently implicated regions than males with autism (Figure 2; Figure S11). This suggests that females with autism might constitute a less heterogeneous group than males with autism, who show less pronounced overlap of focal atypicalities in laterality. Also, when considering males and females separately, atypical asymmetry was associated with more social-communicative symptoms only in males with autism, but not in females with autism, suggesting that phenotypically similar manifestations of atypical lateralization appear to have differential cognitive implications for males and females with autism.

We found that both extreme left- and rightward deviations were associated with LD, but only rightward deviations differentiated individuals with autism with and without LD from each other. This is in line with prior reports (17,30). Two structural studies further showed differential morphological alterations in individuals with autism with different developmental language profiles (73) and a loss of leftward asymmetry in the arcuate fasciculus in nonverbal children with autism (74). The degree of atypical rightward lateralization may thus constitute a biological marker of different etiological subgroups with different language profiles in autism. Evidence suggests that onset of language before the age of 2 years (75) and the level of language at the ages 5 and 6 years (76) predict functional outcome later in life in autism. Developing stratification markers based on LD will thus have important clinical implications for early prognosis, individualized diagnoses, and early language-based interventions in individuals at risk. Other important factors, such as handedness, seemed to have less influence on extreme deviations, which was corroborated by a range of control analyses and is in line with prior accounts (62,77). It is likely that atypical brain asymmetry and handedness share common underlying mechanisms in autism; however, there seems to be no systematic, straightforward relationship, as atypical asymmetry has repeatedly been reported in right-handed individuals, too (24,78,79).

Strengths and Limitations

We present analyses in a large-scale, deeply phenotyped, and prospectively harmonized dataset. Results are robust across several analyses addressing potential confounds and are overall also observable in the large-scale, though not harmonized, ABIDE. Replicability and robustness of findings are important prerequisites as a first step toward establishing neural biomarkers.

Nevertheless, our findings should be considered in light of some limitations. First, despite the large dataset, when dividing individuals by diagnostic group, sex, LD, and site, subsamples decrease substantially in size. While our Bayesian Gaussian process regression model adapts to the availability of data [i.e., gives more conservative estimates when data density decreases (33)], the model would yield more precise estimates with larger sample sizes. Second, large datasets come at the

expense of additional confounds associated with site. We addressed this by both including site in the model and running an alternative method for controlling batch effects. Our results are robust, but residual site effects cannot fully be excluded. Third, the question arises whether there are also experience-dependent influences on cortical asymmetry. Longitudinal analyses are needed to pinpoint the onset and trajectory of atypical development in subgroups on the autism spectrum. Fourth, the normative modeling approach is suitable for detecting extreme deviations from a normative pattern. However, an alternative hypothesis that individuals with autism might lack specialization of either hemisphere (68), which would be expressed in reduced laterality, might be less detected with the current approach.

Conclusions

We estimated a normative model of gray matter voxelwise asymmetry based on a large neurotypical cohort and applied this to a large, deeply phenotyped, and heterogeneous autism sample. Our results confirm that atypical asymmetry is a core feature of the autism neurophenotype, shows highly individualized patterns across individuals and is differentially related to different symptom profiles, such as LD. Further exploration of such associations has the potential to yield clinically relevant stratification markers needed for precision medicine.

ACKNOWLEDGMENTS AND DISCLOSURES

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under Grant Agreement Nos 115300 (for EU-AIMS) and 777394 (for AIMS-2-TRIALS). This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Programme, the European Federation of Pharmaceutical Industries and Associations, Autism Speaks, Autistica, and the Simons Foundation Autism Research Initiative. This work was also supported by the Netherlands Organisation for Scientific Research through Vidi grants (Grant Nos. 864.12.003 [to CFB] and 016.156.415 [to AM]), the Seventh Framework Programme (Grant Nos. 602805 [AGGRESSOTYPE] [to JKB], 603016 [MATRICS] [to JKB], and 278948 [TACTICS] [to JKB]), and the European Community's Horizon 2020 Programme (H2020/2014-2020) (Grant Nos. 643051 [MiND] and 642996 [BRAINVIEW]). This work also received funding from the Wellcome Trust U.K. Strategic Award (Award No 098369/Z/12/Z) and the National Institute for Health Research Maudsley Biomedical Research Centre (to DGMM). TW gratefully acknowledges grant support from the Niels Stensen Fellowship. NEH gratefully acknowledges grant support from the German Research Foundation (Grant Nos. DFG HO 5674/2-1 and GRK2350/1) and the Olympia Morata Program of the University of Heidelberg. SB-C was funded by the Autism Research Trust, the Wellcome Trust, the Templeton World Charitable Foundation, and the National Institute for Health Research Biomedical Research Centre in Cambridge during the period of this work.

TC has received consultancy fees from Roche and book royalties from Guildford Press and Sage. TB served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg, Shire, and Infectopharm, received conference support or speaker's fees from Lilly, Medice, and Shire, and received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press; the present work is unrelated to these relationships. DGMM has been a consultant to and advisory board member for Roche and Servier; he is not an employee of nor stock shareholder in any of these companies. JKB has been a consultant to, advisory board member of, and speaker for Takeda/Shire, Medice, Roche, and Servier; he is not an employee of nor stock shareholder in any of these companies. He has no other financial or material support, including expert testimony, patents, or royalties. CFB is director and shareholder in SBGneuro. The other authors report no biomedical financial interests or potential conflicts of interest.

We thank all participants and their families for participating in this study. We also gratefully acknowledge the contributions of all members of the EU-AIMS LEAP group.

ARTICLE INFORMATION

From Donders Institute for Brain, Cognition, and Behavior (DLF, TW, MZ, MPZ, AM, JKB, CFB), Radboud University Nijmegen; Department of Cognitive Neuroscience (DLF, MZ AM, JKB, CFB), Radboud University Medical Center Nijmegen; Karakter Child and Adolescent Psychiatry University Centre (JKB), Nijmegen; and Department of Psychiatry (SD), Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; Department of Psychology (TW), University of Oslo; Norwegian Center for Mental Disorders Research (NORMENT) (TW), Division of Mental Health and Addiction, University of Oslo Hospital and Oslo University Hospital, Oslo, Norway; Department of Child and Adolescent Psychiatry and Psychotherapy (NEH, TB), Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim; Department of Psychiatry and Psychotherapy (CM), Central Institute of Mental Health, University of Heidelberg, Mannheim; and Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy (CE), University Hospital Frankfurt am Main, Goethe University, Frankfurt, Germany; Department of Psychology (TC, JT, CE), Sackler Institute for Translational Neurodevelopment (FD, EL, DGMM), Department of Neuroimaging (AM), and Department of Forensic and Neurodevelopmental Sciences (FD, EL, DGMM), Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London; Autism Research Centre (SB-C, RH), Department of Psychiatry, University of Cambridge, Cambridge; and Centre for Functional MRI of the Brain (CFB), University of Oxford, Oxford, United Kingdom; and Department of Applied Psychology: Health, Development, Enhancement, and Intervention (JT), University of Vienna, Vienna, Austria.

Members of the EU-AIMS LEAP group: Jumana Ahmad, Sara Ambrosino, Bonnie Auyeung, Tobias Banaschewski, Simon Baron-Cohen, Sarah Baumeister, Christian F. Beckmann, Sven Bölte, Thomas Bourgeron, Carsten Bours, Michael Brammer, Daniel Brandeis, Claudia Brogna, Yvette de Bruijn, Jan K. Buitelaar, Bhismadev Chakrabarti, Tony Charman, Ineke Cornelissen, Daisy Crawley, Flavio Dell'Acqua, Guillaume Dumas, Sarah Durston, Christine Ecker, Jessica Faulkner, Vincent Frouin, Pilar Garcés, David Goyard, Lindsay Ham, Hannah Hayward, Joerg Hipp, Rosemary Holt, Mark H. Johnson, Emily J.H. Jones, Prantik Kundu, Meng-Chuan Lai, Xavier Liogier d'Ardhuy, Michael V. Lombardo, Eva Loth, David J. Lythgoe, René Mandl, Andre Marquand, Luke Mason, Maarten Mennes, Andreas Meyer-Lindenberg, Carolin Moessnang, Nico Mueller, Declan G.M. Murphy, Bethany Oakley, Laurence O'Dwyer, Marianne Oldehinkel, Bob Oranje, Gahan Pandina, Antonio M. Persico, Barbara Ruggeri, Amber Ruigrok, Jessica Sabet, Roberto Sacco, Antonia San José Cáceres, Emily Simonoff, Will Spooren, Julian Tillmann, Roberto Toro, Heike Tost, Jack Waldman, Steve C.R. Williams, Caroline Wooldridge, and Marcel P. Zwiers.

Address correspondence to Dorothea L. Floris, Ph.D., at d.floris@donders.ru.nl.

Received Jul 6, 2020; revised and accepted Aug 18, 2020.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2020.08.008.

REFERENCES

1. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington: American Psychiatric Association.
2. Lombardo MV, Lai MC, Baron-Cohen S (2019): Big data approaches to decomposing heterogeneity across the autism spectrum. Mol Psychiatry 24:1435–1450.
3. Lenroot RK, Yeung PK (2013): Heterogeneity within autism spectrum disorders: What have we learned from neuroimaging studies? Front Hum Neurosci 7:773.
4. Lindell AK, Hudry K (2013): Atypicalities in cortical structure, handedness, and functional lateralization for language in autism spectrum disorders. Neuropsychol Rev 23:257–270.

5. Floris DL, Howells H (2018): Chapter 8—Atypical structural and functional motor networks in autism. Prog Brain Res 238:207–248.
6. Gazzaniga MS (1995): Principles of human brain organization derived from split-brain studies. Neuron 14:217–228.
7. Rogers LJ, Zucca P, Vallortigara G (2004): Advantages of having a lateralized brain. Proc Biol Sci 271(suppl):S420–422.
8. Springer SP, Deutsch G (1997): Left Brain, Right Brain: Perspectives From Cognitive Neuroscience, 5th ed. W.H. Freeman and Company/Worth Publishers.
9. Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001): Cerebral asymmetry and the effects of sex and handedness on brain structure: A voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage 14:685–700.
10. Jäncke L, Schlaug G, Huang Y, Steinmetz H (1994): Asymmetry of the planum parietale. Neuroreport 5:1161–1163.
11. Prior MR, Bradshaw JL (1979): Hemisphere functioning in autistic children. Cortex 15:73–81.
12. Postema MC, van Rooij D, Anagnostou E, Arango C, Auzias G, Behrmann M, *et al.* (2019): Altered structural brain asymmetry in autism spectrum disorder in a study of 54 datasets. Nat Commun 10:4958.
13. Preslar J, Kushner HI, Marino L, Pearce B (2014): Autism, lateralisation, and handedness: A review of the literature and meta-analysis. Laterality 19:64–95.
14. Kong XZ, Postema MC, Guadalupe T, de Kovel C, Boedhoe PSW, Hoogman M, *et al.* (2020): Mapping brain asymmetry in health and disease through the ENIGMA consortium [published online ahead of print May 18]. Hum Brain Mapp.
15. Floris DL, Barber AD, Nebel MB, Martinelli M, Lai MC, 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.
16. Floris DL, Chura LR, Holt RJ, Suckling J, Bullmore ET, Baron-Cohen S, Spencer MD (2013): Psychological correlates of handedness and corpus callosum asymmetry in autism: The left hemisphere dysfunction theory revisited. J Autism Dev Disord 43:1758–1772.
17. Floris DL, Lai M-C, Auer T, Lombardo MV, Ecker C, Chakrabarti B, *et al.* (2016): Atypically rightward cerebral asymmetry in male adults with autism stratifies individuals with and without language delay. Hum Brain Mapp 37:230–253.
18. Herbert MR, Harris GJ, Adrien KT, Ziegler DA, Makris N, Kennedy DN, *et al.* (2002): Abnormal asymmetry in language association cortex in autism. Ann Neurol 52:588–596.
19. De Fossé L, Hodge SM, Makris N, Kennedy DN, Caviness VS, McGrath L, *et al.* (2004): Language-association cortex asymmetry in autism and specific language impairment. Ann Neurol 56:757–766.
20. Rojas DC, Camou SL, Reite ML, Rogers SJ (2005): Planum temporale volume in children and adolescents with autism. J Autism Dev Disord 35:479–486.
21. Rojas DC, Bawn SD, Benkers TL, Reite ML, Rogers SJ (2002): Smaller left hemisphere planum temporale in adults with autistic disorder. Neurosci Lett 328:237–240.
22. Lange N, Dubray MB, Lee JE, Froimowitz MP, Froehlich A, Adluru N, *et al.* (2010): Atypical diffusion tensor hemispheric asymmetry in autism. Autism Res 3:350–358.
23. Brown TT, Lugar HM, Coalson RS, Miezin FM, Petersen SE, Schlaggar BL (2005): Developmental changes in human cerebral functional organization for word generation. Cereb Cortex 15:275–290.
24. Flagg EJ, Cardy JEO, Roberts W, Roberts TPL (2005): Language lateralization development in children with autism: Insights from the late field magnetoencephalogram. Neurosci Lett 386:82–87.
25. Kansaku K, Kitazawa S (2001): Imaging studies on sex differences in the lateralization of language. Neurosci Res 41:333–337.
26. Hirnstein M, Hugdahl K, Hausmann M (2019): Cognitive sex differences and hemispheric asymmetry: A critical review of 40 years of research. Laterality 24:204–252.
27. Toga AW, Thompson PM (2003): Mapping brain asymmetry. Nat Rev Neurosci 4:37–48.
28. Papadatou-Pastou M (2011): Handedness and language lateralization: Why are we right-handed and left-brained? Hell J Psychol 8:248–265.
29. Markou P, Ahtam B, Papadatou-Pastou M (2017): Elevated levels of atypical handedness in autism: Meta-analyses. Neuropsychol Rev 27:258–283.
30. Escalante-Mead PR, Minshew NJ, Sweeney JA (2003): Abnormal brain lateralization in high-functioning autism. J Autism Dev Disord 33:539–543.
31. Wolfers T, Floris DL, Dinga R, van Rooij D, Isakoglou C, Kia SM, *et al.* (2019): From pattern classification to stratification: Toward conceptualizing the heterogeneity of autism spectrum disorder. Neurosci Biobehav Rev 104:240–254.
32. Wolfers T, Doan NT, Kaufmann T, Alnæs D, Moberget T, Agartz I, *et al.* (2018): Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. JAMA Psychiatry 75:1146–1155.
33. Marquand AF, Kia SM, Zabihi M, Wolfers T, Buitelaar JK, Beckmann CF (2019): Conceptualizing mental disorders as deviations from normative functioning. Mol Psychiatry 24:1415–1424.
34. Zabihi M, Oldehinkel M, Wolfers T, Frouin V, Goyard D, Loth E, *et al.* (2019): Dissecting the heterogeneous cortical anatomy of autism spectrum disorder using normative models. Biol Psychiatry Cogn Neurosci Neuroimaging 4:567–578.
35. 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.
36. Loth E, Charman T, Mason L, Tillmann J, Jones EJH, Wooldridge C, *et al.* (2017): The EU-AIMS Longitudinal European Autism Project (LEAP): Design and methodologies to identify and validate stratification biomarkers for autism spectrum disorders. Mol Autism 8:24.
37. Oldehinkel M, Mennes M, Marquand A, Charman T, Tillmann J, Ecker C, *et al.* (2019): Altered connectivity between cerebellum, visual, and sensory-motor networks in autism spectrum disorder: Results from the EU-AIMS Longitudinal European Autism Project. Biol Psychiatry Cogn Neurosci Neuroimaging 4:260–270.
38. Floris DL, Filho JOA, Lai M-C, Giavasis S, Oldehinkel M, Mennes M, *et al.* (2021): Towards robust and replicable sex differences in the intrinsic brain function of autism. Mol Autism 12:19.
39. Holiga Š, Hipp JF, Chatham CH, Garces P, Spooren W, d'Ardhuy XL, *et al.* (2019): Patients with autism spectrum disorders display reproducible functional connectivity alterations. Sci Transl Med 11(481):eaat9223.
40. Mei T, Llera A, Floris DL, Forde NJ, Tillmann J, Durston S, *et al.* (2020): Gray matter covariations and core symptoms of autism. The EU-AIMS Longitudinal European Autism Project. Mol Autism 11:86.
41. Baumeister S, Moessnang C, Bast N, Hohmann S, Tillmann J, Goyard D, *et al.* (2020): Attenuated anticipation of social and monetary rewards in autism spectrum disorders. bioRxiv. https://doi.org/10.1101/2020.07.06.186650.
42. Moessnang C, Baumeister S, Tillmann J, Goyard D, Charman T, Ambrosino S, *et al.* (2020): Social brain activation during mentalizing in a large autism cohort: The Longitudinal European Autism Project. Mol Autism 11:17.
43. Marquand AF, Wolfers T, Mennes M, Buitelaar J, Beckmann CF (2016): Beyond lumping and splitting: A review of computational approaches for stratifying psychiatric disorders. Biol Psychiatry Cogn Neurosci Neuroimaging 1:433–447.
44. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, *et al.* (2000): The Autism Diagnostic Observation Schedule—Generic: A standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30:205–223.
45. Lord C, Rutter M, le Couteur A (1994): Autism Diagnostic Interview—Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.

46. Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh Inventory. Neuropsychologia 9:97–113.
47. Kurth F, Mackenzie-Graham A, Toga AW, Luders E (2014): Shifting brain asymmetry: The link between meditation and structural lateralization. Soc Cogn Affect Neurosci 10:55–61.
48. Kurth F, Gaser C, Luders E (2015): A 12-step user guide for analyzing voxel-wise gray matter asymmetries in statistical parametric mapping (SPM). Nat Protoc 10:293–304.
49. Ashburner J (2007): A fast diffeomorphic image registration algorithm. Neuroimage 38:95–113.
50. 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.
51. Wolfers T, Beckmann CF, Hoogman M, Buitelaar JK, Franke B, Marquand AF (2019): Individual differences v. The average patient: Mapping the heterogeneity in ADHD using normative models. Psychol Med 50:314–323.
52. Rezek I, Beckmann CF (2012): Models of disease spectra. arXiv. 1207.4674.
53. Rasmussen CE, Williams CKI (2006): Model selection and adaptation of hyperparameters. In: Rasmussen CE, Williams CKI. Gaussian Processes for Machine Learning. Cambridge, MA: MIT Press.
54. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, *et al.* (2004): Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(suppl 1):S208–219.
55. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD (2011): Large-scale automated synthesis of human functional neuroimaging data. Nat Methods 8:665–670.
56. Sen PK, Lindeman RH, Merenda PF, Gold RZ (1981): Introduction to bivariate and multivariate analysis. J Am Stat Assoc 76(375):752.
57. Nielson DM, Pereira F, Zheng CY, Migineishvili N, Lee JA, Thomas AG, Bandettini PA (2018): Detecting and harmonizing scanner differences in the ABCD study—Annual release 1.0. bioRxiv. https://doi.org/10.1101/309260.
58. Benjamini Y, Hochberg Y (2000): On the adaptive control of the false discovery rate in multiple testing with independent statistics. J Educ Behav Stat 25:60–83.
59. Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, *et al.* (2014): The Autism Brain Imaging Data Exchange: Towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry 19:659–667.
60. Di Martino A, O'Connor D, Chen B, Alaerts K, Anderson JS, Assaf M, *et al.* (2017): Enhancing studies of the connectome in autism using the Autism Brain Imaging Data Exchange II. Sci Data 4:170010.
61. Tang S, Sun N, Floris DL, Zhang X, Di Martino A, Yeo BTT (2019): Reconciling dimensional and categorical models of autism heterogeneity: A brain connectomics and behavioral study. Biol Psychiatry 87:1071–1082.
62. Kong XZ, Mathias SR, Guadalupe T, Abé C, Agartz I, Akudjedu TN, *et al.* (2018): Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide via the ENIGMA consortium. Proc Natl Acad Sci U S A 115:E5154–5163.
63. Sun T, Patoine C, Abu-Khalil A, Visvader J, Sum E, Cherry TJ, *et al.* (2005): Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. Science 308:1794–1798.
64. Baron-Cohen S, Tsompanidis A, Auyeung B, Nørgaard-Pedersen B, Hougaard DM, Abdallah M, *et al.* (2020): Foetal oestrogens and autism. Mol Psychiatry 25:2970–2978.
65. Geschwind DH, Miller BL, DeCarli C, Carmelli D (2002): Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. Proc Natl Acad Sci U S A 99:3176–3181.
66. Geschwind N, Behan P (1982): Left-handedness: Association with immune disease, migraine, and developmental learning disorder. Proc Natl Acad Sci U S A 79:5097–5100.
67. Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Kennedy DN, Filipek PA, *et al.* (2005): Brain asymmetries in autism and developmental language disorder: A nested whole-brain analysis. Brain 128:213–226.
68. Nebel MB, Joel SE, Muschelli J, Barber AD, Caffo BS, Pekar JJ, Mostofsky SH (2014): Disruption of functional organization within the primary motor cortex in children with autism. Hum Brain Mapp 35:567–580.
69. Thompson A, Murphy D, Dell'Acqua F, Ecker C, McAlonan G, Howells H, *et al.* (2017): Impaired communication between the motor and somatosensory homunculus is associated with poor manual dexterity in autism spectrum disorder. Biol Psychiatry 81:211–219.
70. Kana RK, Liu Y, Williams DL, Keller TA, Schipul SE, Minshew NJ, Just MA (2013): The local, global, and neural aspects of visuospatial processing in autism spectrum disorders. Neuropsychologia 51:2995–3003.
71. Gauthier I, Tarr MJ, Moylan J, Skudlarski P, Gore JC, Anderson AW (2000): The fusiform "face area" is part of a network that processes faces at the individual level. J Cogn Neurosci 12:495–504.
72. Coffman MC, Anderson LC, Naples AJ, McPartland JC (2013): Sex differences in social perception in children with ASD. J Autism Dev Disord 45:589–599.
73. Lai M-C, Lombardo MV, Ecker C, Chakrabarti B, Suckling J, Bullmore ET, *et al.* (2014): Neuroanatomy of individual differences in language in adult males with autism. Cereb Cortex 25:3613–3628.
74. Wan CY, Marchina S, Norton A, Schlaug G (2012): Atypical hemispheric asymmetry in the arcuate fasciculus of completely nonverbal children with autism. Ann N Y Acad Sci 1252:332–337.
75. Mayo J, Chlebowski C, Fein DA, Eigsti I-M (2013): Age of first words predicts cognitive ability and adaptive skills in children with ASD. J Autism Dev Disord 43:253–264.
76. Howlin P (2003): Outcome in high-functioning adults with autism with and without early language delays: Implications for the differentiation between autism and Asperger syndrome. J Autism Dev Disord 33:3–13.
77. Pearson A, Hodgetts S (2020): Can cerebral lateralisation explain heterogeneity in language and increased nonright handedness in autism? A literature review. Res Dev Disabil 105:103738.
78. Braeutigam S, Swithenby SJ, Bailey AJ (2008): Contextual integration the unusual way: A magnetoencephalographic study of responses to semantic violation in individuals with autism spectrum disorders. Eur J Neurosci 27:1026–1036.
79. Pijnacker J, Geurts B, van Lambalgen M, Buitelaar J, Hagoort P (2010): Exceptions and anomalies: An ERP study on context sensitivity in autism. Neuropsychologia 48:2940–2951.