Default Mode and Fronto-Parietal Network Associations with IQ Development Across Childhood in Autism

Joshua K Lee (✉ jkilee@ucdavis.edu)

University of California Davis MIND Institute <https://orcid.org/0000-0002-0479-0156>

An Chuen Billy Cho

University of California Davis MIND Institute

Derek S Andrews

University of California Davis MIND Institute

Sally Ozonoff

University of California Davis MIND Institute

Sally J Rogers

University of California Davis MIND Institute

David G Amaral

University of California Davis MIND Institute

Marjorie Solomon

University of California Davis MIND Institute

Christine Wu Nordahl

University of California Davis MIND Institute

Research Article

Keywords: autism spectrum disorder, intellectual disability, IQ, MRI, longitudinal, default mode, fronto-parietal

Posted Date: November 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1033421/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Intellectual disability affects approximately one third of individuals with autism spectrum disorder (autism), yet a major unresolved question remains concerning the neurobiology that differentiates autistic individuals with and without intellectual disability. IQ is highly variable during childhood. We previously identified subgroups of autistic children with different trajectories of intellectual development from early childhood (2-3½ years) up to middle childhood (9-12 years): (a) Persistently-High: Individuals whose intelligence quotients (IQs) remained in the average or better range during this period, (b) Persistently-Low: Individuals whose IQs remained in the range of intellectual disability (IQ < 70) throughout development, and (c) Changers: Individuals whose IQs began in the range of intellectual disability but increased to the borderline or normal IQ range by middle childhood. In the present research, we sought to identify neurobiology that differentiates these trajectory-defined groups within our autism cohort in two brain networks with established links to intellectual functioning and its impairment in (1) the frontoparietal network (FPN), and (2) the default mode network (DMN).

Methods: We conducted multivariate distance matrix regression (MDMR) and effect size analyses to examine the volumes of 22 brain regions (11 regions x 2 hemispheres) within the FPN and 24 (12 regions x 2 hemispheres) within the DMN in 48 Persistently-High (18 female), 108 Persistently-Low (32 female), and 109 Changers (39 female) using structural MRI that had been acquired at baseline, and IQ measurements from up to three time points spanning early to middle childhood (Mean Age Time 1: 3.2 years; Time 2: 5.4 years; Time 3: 11.3 years). FPN and DMN network regions of interest were defined on the basis of the large-scale networks defined in Smith et al., (2009).

Results: Changers exhibited different DMN network structure from both Persistently-Low and Persistently-High trajectory groups at baseline, but the Persistently-High did not differ from the Persistently-Low group, suggesting that DMN structure may be an early predictor for change in IQ trajectory across childhood. In contrast, Persistently-High exhibited differences in the FPN from both Persistently-Low and Changers groups at baseline, suggesting a difference related more to concurrent IQ and the absence of intellectual disability.

Conclusions: Within autism, DMN structure at baseline may differentiate individuals with persistently low IQ from those with more transitory low IQ that improves to the borderline range or better through early childhood, potentially indicating compensatory mechanisms which may be targeted by future interventions. The brain structure differences between these three IQ-based subgroups may be indicative of distinct neural underpinnings of autism phenotypic subtypes.

Background

Intellectual functioning, as assessed using standardized intelligence quotients (IQ) or developmental quotients (DQ), which are henceforth both referred to as IQ, is highly variable in autistic children. The CDC estimates that 33% of autistic children have IQs in the range of intellectual disability (IQ < 70), 24% in the

borderline IQ range of 70-85, and 42% with average or higher IQs (>85) (1). Moreover, the trajectory of intellectual functioning across childhood is also highly variable (2–4). We recently investigated change in IQ scores from 3 to 8 years of age and identified four autistic subgroups: two groups, comprising 26% and 18% of the sample respectively, had mean IQs in the intellectual disability range at both time points (one lower, one higher); a third group (22%) had IQs in the average range or better at both time points. Of particular interest was a fourth group, comprising roughly one third of the cohort (35%), that started with IQs in the intellectual disability range but made significant gains (average of 34 points) to have IQs in the average range by age 6-8 (5).

One of the major unresolved questions concerning the neurobiology of autism is what differentiates autistic individuals with and without intellectual disability. Identification of neural predictors of different IQ trajectories could be useful in guiding development of interventions or providing early clues to parents for planning access to services and supports. While there have been hundreds of MRI studies of brain organization in autism, an incredibly small number have examined children with IQs below 85. A 2016 query of the National Database for Autism Research found that out of 47,400 total participants with autism, only 11% had IQs less than 85 and <1% of these had neuroimaging data available (6). Accordingly, autistic individuals with intellectual disability are understudied, and very little is known about if and how their brains develop differently from autistic children without ID.

One notable exception is Reiter et al (7) who found resting state fMRI patterns of network organization were different between groups of autistic children (6-15 years) with $IQ \leq 85$ and $IQ \geq 115$. The group with lower IQ demonstrated significant underconnectivity within the default mode network and within the ventral visual stream. Participants with higher FSIQ had reduced network segregation compared to TD. Gabrielsen et al (8) studied 7-17-year-old children with autism, comparing a subgroup with low verbal and cognitive performance (LVCP) with children with normal verbal ability and cognitive performance (NVCP). The LVCP group had decreased within-network connectivity in default, salience, auditory, and frontoparietal networks and decreased interhemispheric connectivity compared to the NVCP group.

In the current study, we evaluated participants from the UC Davis MIND Institute Autism Phenome Project, which follows participants from early childhood at the age of diagnosis through childhood. Recently, in an extension from our previous work (5) which identified IQ trajectory subgroups through 8 years of age in this sample, we utilized latent class growth analysis to subgroup participants based on trajectory of IQ development from 3 to 12 years of age (9). We identified three subgroups: 1) IQ scores in the normal range at across childhood (Persistently-High IQ; P-High), 2) IQ scores in the range of intellectual disability across childhood (Persistently-Low IQ; P-Low), and 3) a group with low IQ in early childhood followed by age increases that plateaued as individuals by age 12 (Changers) (5). Using structural MRI data acquired at baseline, around 3 years of age, we examined structural volumes of key brain regions of the frontoparietal (FPN) and default mode (DMN) networks, key networks supporting intellectual ability functioning (10–14). In this study, we assess associations between the volumes of regions of interest within the FPN and the DMN in early childhood between the IQ trajectory groups using multivariate distance matrix regression (MDMR) (15). MDMR tests for associations between phenotypic variables (e.g. age, sex, IQ

group) and a distance matrix—a pair-wise matrix indicating the degree to which individuals differ across a set of measurements, in the present case, volumes of regions of interest in the FPN and DMN. Complementing this analysis, we conducted MDMR effect-size analysis to assess which brain regions within the FPN and DMN contributed the most to group differences (16).

Given prior evidence of within-network functional connectivity differences between autistic children with and without ID in these two networks, we predicted that volumetric differences in brain regions involved in these networks would be present between the 3 IQ trajectory subgroups. Specifically, we hypothesized that differences in these networks at baseline might predict change in IQ scores across development, and that we would observe differences in FPN and DMN structure between the Changers and P-Low IQ groups.

Methods

Participants

IQ trajectories in the current study were derived from 265 participants (89 female/176 male) diagnosed with autism spectrum disorder whose intellectual ability was assessed at up to two time points in early childhood (T1: Mean: 3.2(0.5) years, and T2, M(SD)= 11.3(1.0)) and a third time point in middle childhood (9-12 years of age; T3). Developmental quotient (DQ) was measured at Time 1 using the Mullen Scales of Early Learning (MSEL)(17), and at Time 2 and Time 3 using the MSEL or the Differential Ability Scale (DAS)(18) (depending on language abilities). To allow longitudinal analysis, T-scores from both the MSEL and DAS subtests were converted to standardized scores with a mean of 100 and standard deviation of 15, and then averaged to obtain an overall standardized score.

Autism was diagnosed by research-reliable clinical psychologists at the Intellectual and Developmental Disabilities Research Center (IDDRC) at the UC Davis MIND Institute using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule (ADOS)-Generic or ADOS-2 (19–22). ADOS CSS ranges from 1 to 10, with higher scores indicating greater autism symptom severity. Participants were English speaking without suspected vision, hearing, or neurological conditions. All research activities were conducted at the University of California Davis MIND Institute and Imaging Research Center and were approved by the UC Davis Institutional Review Board. Parents or legal guardians provided informed consent prior to participation. The data described in the current research is available from the corresponding or senior authors upon reasonable request.

Identification of IQ Trajectory Groups

In recent work(9), we identified three IQ trajectory groups: (1) Persistently-High IQ (P-High): Individuals whose IQs remained within normal range throughout childhood, n=48 (18 female), (2) Persistently-Low IQ (P-Low): Individuals whose IQs remained low in the range of intellectual disability throughout childhood, n=108 (32 female), and (3) Changers: Individuals whose IQs began in the range of intellectual disability but increased over childhood, n=70 (39 female). Mean IQs of each group at baseline and outcome

timepoints are reported in Table 1, as well as other sample characteristics. Briefly, trajectory groups had been identified using latent class growth analysis (13) to identify distinct IQ trajectories in a sample of ASD youth, with age matched TD controls serving as a reference group. All participants with at least one timepoint were included in the analysis ($n_{\text{ASD}}=373$; $n_{\text{TD}}=162$). Linear and quadratic age-based models were tested for the ASD group. Both information-heuristic (e.g., information criterion values) and inferential (e.g., likelihood ratio tests) relative fit comparisons were used to select the best-fitting modeling solution (23). Namely, information-heuristic indices include the Akaike Information Criterion (AIC) (24), Bayesian Information Criterion (BIC) (25), and sample size-adjusted BIC (SBIC) (26), in which lower values indicate better fit, as well as the approximate Bayes Factor (27,28). As an inferential index, the approximate correct model probability (CMP) (25) compares a single model versus all other models under consideration, and models with a CMP >.10 should be considered as candidate models.

Imaging Acquisition and Processing

Structural MRI at T1 were acquired during natural nocturnal sleep (29) on a 3 Tesla Siemens Trio with an 8-channel head-coil, which included a T1-weighted MPRAGE (TR 2,170 ms, TE 4.86 ms, FOV 256, 192 sagittal slices, 1.0 mm slice thickness, 8:46 acquisition time). Spatial inhomogeneity in images were distortion corrected using a calibration phantom acquired at each scan (ADNI MAGPHAM, The Phantom Laboratory; Image Owl, Inc., Greenwich, NY, USA, <http://www.phantomlab.com>) (30). Images were visually assessed for quality and by using a previously described quantitative procedures (31).

Identifiable information was removed from each MPRAGE, defaced, and then uploaded to MRICloud (<https://mricloud.org>) (32) for image segmentation. Gray and white matter labels defined by the LONI Probabilistic Brain Atlas protocol (LPBA40) (33,34) were segmented using multi-atlas image segmentation. Multi-atlas image segmentation registers a set of age-appropriate anatomically labeled atlases onto a target brain image using diffeomorphic registration, which produces a set of candidate segmentations, and consensus segmentations are then produced using joint-label fusion, an advanced voting procedure (35–37).

Network Definitions

Regions of interest for each network were chosen based on established large-scale intrinsic functional connectivity networks (38).

FPN Network

The FPN comprised the following regions of interest: bilateral superior prefrontal gyri, middle frontal gyri, dorsal middle frontal gyri, opercularis of the inferior frontal gyri, orbitalis of the inferior frontal gyri, precentral gyri, supramarginal gyri, angular gyri, precunei, inferior temporal gyri, and the middle occipital gyri.

DMN Network

The DMN comprised the following regions of interest: bilateral posterior cingulate cortices, rostral anterior cingulate cortices, precune, cune, middle temporal gyri, angular gyri, gyri rectus, middle fronto orbital gyri, the prefrontal and poles of the superior frontal gyri, amygdalae, and parahippocampal gyri.

Analytic Strategy

We used multivariate distance matrix regression (MDMR) to identify associations between the identified IQ trajectory groups and the volumes of regions of interest within the FPN and DMN networks at baseline. MDMR is a robust, person-centric, multivariate regression method with application in connectomic, genomic, and ecological research (15,39,40). MDMR regresses a Gower-transformed pair-wise distance matrix onto an explanatory model and residual term (15,41). The distance matrix is an index representing how much individuals differ from one another across a set of outcomes (e.g. brain measurements). When constructing a distance *matrix*, a distance *metric* must be chosen. Here we chose the Manhattan “city-block” distance, as we’ve done previously (39), because it is more robust to extreme values than either Euclidean and Pearson’s distances, and can be a better choice for high-dimensional datasets (42). Interpretation of the results of MDMR regressions is aided by distance-based redundancy analysis, a dimension-reduction technique that aids visualization of multivariate datasets which is constrained on the variables of interest and other covariates (43,44), and by using Euclidean projection to estimate distances between group centroids (45). Finally, we use a bootstrapping technique to estimate relative effect sizes for individual outcomes (e.g., brain regions within the network) to each MDMR result (16,39).

Collectively this procedure allows us to first identify the overall pattern differentiating individuals of different groups (P-High, P-Low, Changers), and then second, to identify specific regions within the network which contribute most to the overall pattern using effect-size analysis. We then follow up and descriptively identify the specific volumetric differences (adjusted for total brain volume) in brain regions exhibiting the greatest effect sizes within each significant MDMR result. MDMR analyses separately examined the FPN and DMN distance matrices which were regressed on the following model: $Y = \beta_0 + \beta_1(\text{IQ trajectory groups}) + \beta_2(\text{age}) + \beta_3(\text{sex})$. Interactions between sex and trajectory groups were also tested.

Results

Sample Characteristics

Table 1 reports sample characteristics. Baseline ADOS CSS significantly differed by trajectory group, $F(2, 115) = 13.4, p < 0.0001$), with the highest CSS scores occurring in the P-Low group. Baseline total brain volume did not differ between trajectory groups, $F(2, 141) = 1.62, p = 0.20$).

MDMR Analysis

We conducted MDMR analyses and associated effect-size analyses on the FPN and DMN at baseline in early childhood.

FPN Network

MDMR analysis demonstrated that FPN volumes in both the Changers ($B = .008, p = .010$) and P-Low ($B = .008, p = .009$) groups significantly differed from the P-High group, but that the P-Low and Changers did not significantly differ from each other ($B = .003, p = .721$) (Figure 1) (Table 2). Regional effect size analysis underlying these group differences are reported in Figure 2. The two largest effect sizes underlying the difference between Changers and P-High groups were smaller left middle occipital gyrus volumes ($\beta = -0.65, SE = 0.17, p = .0002$) and larger left inferior temporal gyrus volumes ($\beta = 0.44, SE = 0.17, p = .011$) in Changers. The two largest effect sizes underlying the difference between P-Low and P-High groups were also smaller left middle occipital gyrus volumes ($\beta = -0.56, SE = 0.17, p = .001$) and larger left inferior temporal gyrus volumes ($\beta = 0.58, SE = 0.17, p = .0009$) in the P-Low group, suggesting similarly sourced differences at baseline within the FPN network. Biological sex also differentiated FPN volumes in autistic individuals ($B = .009, p = 0.003$), although interactions between sex and trajectory groups were not significant ($Bs \leq .005, ps \geq 0.166$). Effect-sizes underlying the sex differences within the FPN are reported in Figure S1a, with the largest effect sizes entailed larger right angular and larger right middle frontal gyri volumes in autistic females than autistic males ($\beta s \geq 0.29, ps \leq .01$).

DMN Network

MDMR analysis demonstrated that both the P-Low ($B = .008, p = .017$) and P-High groups ($B = .007, p = .023$) significantly differed from the Changers group in DMN network structure, but the P-Low and P-High groups did not significantly differ ($B = .004, p = .391$) (Figure 3) (Table 2). Effect size analyses are reported in Figure 4. The two largest effect sizes underlying the difference between Changers and P-Low groups were smaller left ($\beta = -0.42, SE = 0.13, p = .0018$) and right middle temporal gyrus volumes ($\beta = -0.35, SE = 0.13, p = .010$) in Changers. The two largest effect sizes underlying the difference between Changers and P-High groups were smaller right middle temporal gyrus volumes ($\beta = -0.40, SE = 0.17, p = .017$) and smaller left amygdala volumes ($\beta = -0.39, SE = 0.17, p = .025$) in Changers; we do note that the effect sizes distinguishing Changers and P-High groups was relatively more diffuse than was seen in other group comparisons. Biological sex differentiated DMN volumes in autistic individuals ($B = .007, p = 0.03$), but interactions with sex were not significant ($Bs \leq .004, ps \geq 0.498$). Effect-sizes underlying the sex differences are reported in Figure S1b. The two brain regions with the largest effect sizes were larger right angular and right parahippocampal gyri volumes (adjusted for total brain volume) in females, which was confirmed in regression analysis ($\beta s \geq 0.29$ Z-score, $ps \leq 0.025$). Notably, the angular gyrus is one of several shared brain regions between the FPN and DMN networks.

Discussion

The heterogeneous presentations of autism, especially with regard to co-occurring intellectual disability, is sorely problematic in research and clinical practice. Despite an estimated one-third of autistic individuals demonstrating mild to severe intellectual disability, there has been very few studies investigating the phenotypic differences between autistic individuals with and without intellectual

disability, their developmental trajectories, and the ensuing life-course implications. Our prior research identified three distinct IQ trajectories for autistic individuals from ages 2 to 12 years old(9). The present study is the first structural imaging study examining ASD subgroups with differential IQ developmental trajectories. Our aim was to identify the neurobiology which differentiates the three empirically-extracted subgroups. The present findings confirm our hypothesis that volumetric differences in brain regions of the FPN and DMN at baseline would be present between IQ change subgroups. Namely, our multivariate analyses found differences between the P-High subgroup versus the other two subgroups (Changers, P-Low) in the FPN and differences between the Changers subgroups versus the other two subgroups (P-High, P-Low) in the DMN.

Networks Supporting Intellectual Ability and its Impairment

The literature of the neural bases of intelligence has long focused on the FPN (also referred to as the central-executive network) (14), a task-positive network that exhibits increased functional BOLD activation and connectivity with increasing cognitive load across a wide-array of tasks involving multiple demands (12,14,46). More recently, there has been growing interest in the role of the DMN in supporting general intellectual functioning. In contrast to the FPN, the DMN is a task-negative network whose activations tend to be anti-correlated with those of the FPN, the strength of which has been associated with individual differences in IQ measures (10,47,48). Large numbers of imaging studies have examined the neural correlates of intellectual functioning within the normal range, however very little has been published investigating the etiology of intellectual impairment outside of specific patient populations such as in Down Syndrome and Williams Syndrome (49,50). The extant non-autism research frequently reports altered connectivity between the FPN and DMN, for example in Down Syndrome and Williams Syndrome (50), as well as alterations to gray matter density in the dorsal medial prefrontal cortex and other regions within the FPN (51). Several studies have examined the neural correlates of IQ within the normal range in autism, which highlighted the roles of FPN regions (52,53).

In the FPN network, both P-Low and Changers subgroups differed from P-High in left inferior temporal and left middle occipital gyri. These regions are broadly implicated in supporting language, semantic knowledge, and sensory integration, including visual information and object recognition, which may suggest that low IQ in early childhood may be associated with alterations to processes of sensory and perceptual integration.

In the DMN network, both P-Low and P-High groups differed from the Changers group, indicating that the DMN may be the site of developmental compensatory mechanisms, perhaps originating in the middle temporal gyrus, as indicated by its prominence in the effect-size analyses. The middle temporal gyri are notable in that they too subserve language function, semantic knowledge processing, and sensory integration, perhaps an adaption to the differences in inferior temporal and middle occipital that serve functions broadly related.

Research and Clinical Implications

Intellectual disability and other psychiatric and physiological comorbidities do not occur evenly in the autism population, suggesting the presence of autism subtypes with distinct clinical profiles and etiologies (54). In our recent work(9), we demonstrated that the three identified IQ trajectory autism subgroups also presented unique trajectories in autism symptom severity, adaptive functioning, and internalizing and externalizing characteristics. It may be possible that the present findings not only serve as evidence of neurobiological differences between the IQ trajectory subgroups, but also as endophenotypes linked to the expression and severity level of clinical characteristics, or perhaps even indicative of potential ASD subtypes (55). As such, this study adds a piece of neurobiological evidence to the burgeoning literature which suggests *some* forms of autism are etiologically tied to intellectual disability (56). While only a small piece of the puzzle, this study contributes to the distal goals of early clinical screening and intervention, in which a better understanding of an autistic child's clinical profile and developmental trajectories can be met with a personalized, targeted treatment plan.

This research has several strengths. The use of empirically extracted subgroups based on longitudinal measurements of IQ in childhood to look at brain differences is both novel and innovative; moreover, with clear clinical and quality-of-life implications. Another strength is the use of a person-centric multivariate approach, which allowed us to examine differences across whole networks, while effect-size analyses allowed us to identify regions within the network which showed the largest differences. Another strength of this research is However, several limitations merit consideration. First, while we used IQ groupings defined on the basis of longitudinal change in IQ over childhood, we only examined volumetric differences in brain structure between these groups at time of study enrollment in early childhood. This was motivated by a desire to identify early neural predictors of subsequent behavioral change. Nevertheless, future research should examine the full relationship between concurrent changes in both brain and behavior. Another limitation of this research is only volumes lying within the canonical-defined FPN and DMN networks were assessed. It is possible that one or more of these subgroups have FPN or DMN network topology that extends past the boundaries defined by the canonical network, and thus were not considered. A final limitation that we acknowledge is that our individual regions of interest were defined by the LONI parcellation(32). However, other parcellations schemes could have been employed, which may have potentially led to different results, depending on the optimal degree of regional specificity. Future research should employ multiple parcellation schemes to provide both evidence for robustness of results, but also the optimal size of FPN and DMN parcellations. A final limitation of this research is that we lacked an additional out-of-sample longitudinal cohort on which we could test the robustness and replicability of the differences in the FPN and DMN we report here.

Conclusions

The structural brain differences reported here validate three empirically derived, IQ trajectory subgroups with biological bases in brain networks most associated with intellectual functioning. The default mode network may play a key role in differentiating individuals with persistently low IQ from those with more transitory low IQ that improve to moderate IQ through childhood, which is potentially indicative of successful compensatory processes which may be targeted by future interventions.

Declarations

Ethical Approval and Consent to participate

All research was approved by the University of California, Davis Institutional Review Board. Informed Consent was acquired prior to all research activities.

Consent for Publication

Not applicable

Availability of data and materials

Data described in this research is available from the corresponding author on reasonable request.

Competing interests

Dr. Amaral is on the Scientific Advisory Boards of Stemina Biomarkers Discovery, Inc. and Axial Therapeutics. All other authors have no competing interests to declare.

Funding

Funding for this study was provided by the National Institute of Mental Health R01MH104438, R01MH103284, R01MH103371 and the UC Davis MIND Institute Intellectual and Developmental Disabilities Research Center (P50HD103526) and Autism Center of Excellence (P50HD093079), and (AIR-P support). This project was also supported in part by the health resources and services administration (HRSA) of the U.S. Department of health and human services (HHS) under the autism intervention research network on physical health (AIR-P) grant, UT2MC39440. The information, content and/or conclusions are those of the authors and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.

Authors' contributions

Joshua K. Lee and An Chuen Billy Cho equally contributed to the manuscript, research design and analysis. Derek S. Andrews contributed to manuscript and analysis. Christine Nordahl and Marjorie Solomon serve as co-senior investigators, and conceived of research. Sally Rogers and David G. Amaral also conceived of research.

Acknowledgements

Many individuals assisted in data collection in support of this manuscript, including Alexa Hechtman, Axie Acosta, and Brianna Heath. Many thanks to the participants and their families.

References

1. Maenner MJ. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years – Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. *MMWR Surveill Summ* [Internet]. 2020 [cited 2020 Aug 18];69. Available from: <https://www.cdc.gov/mmwr/volumes/69/ss/ss6904a1.htm>
2. Pickles A, Anderson DK, Lord C. Heterogeneity and plasticity in the development of language: a 17-year follow-up of children referred early for possible autism. *J Child Psychol Psychiatry*. 2014;55(12):1354–62.
3. Fountain C, Winter AS, Bearman PS. Six Developmental Trajectories Characterize Children With Autism. *Pediatrics*. 2012 May 1;129(5):e1112–20.
4. Baghdadli A, Assouline B, Sonié S, Pernon E, Darrou C, Michelon C, et al. Developmental Trajectories of Adaptive Behaviors from Early Childhood to Adolescence in a Cohort of 152 Children with Autism Spectrum Disorders. *J Autism Dev Disord*. 2012 Jul 1;42(7):1314–25.
5. Solomon M, Iosif AM, Reinhardt VP, Libero LE, Nordahl CW, Ozonoff S, et al. What will my child's future hold? phenotypes of intellectual development in 2–8-year-olds with autism spectrum disorder. *Autism Res*. 2018;11(1):121–32.
6. Jack A, A. Pelphrey K. Annual Research Review: Understudied populations within the autism spectrum – current trends and future directions in neuroimaging research. *J Child Psychol Psychiatry*. 2017;58(4):411–35.
7. Reiter MA, Mash LE, Linke AC, Fong CH, Fishman I, Müller R-A. Distinct Patterns of Atypical Functional Connectivity in Lower-Functioning Autism. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2019 Mar;4(3):251–9.
8. Gabrielsen TP, Anderson JS, Stephenson KG, Beck J, King JB, Kellems R, et al. Functional MRI connectivity of children with autism and low verbal and cognitive performance. *Mol Autism*. 2018;9:67.
9. Solomon M. IQ phenotypes of autistic youth from early childhood to preadolescence. In: *Virtual Keynote*. 2021.
10. DeSerisy M, Ramphal B, Pagliaccio D, Raffanella E, Tau G, Marsh R, et al. Frontoparietal and default mode network connectivity varies with age and intelligence. *Dev Cogn Neurosci*. 2021 Apr 1;48:100928.
11. Dixon ML, Vega ADL, Mills C, Andrews-Hanna J, Spreng RN, Cole MW, et al. Heterogeneity within the frontoparietal control network and its relationship to the default and dorsal attention networks. *Proc Natl Acad Sci*. 2018 Feb 13;115(7):E1598–607.
12. Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn Sci*. 2010 Apr;14(4):172–9.
13. Jung T, Wickrama K a. S. An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Soc Personal Psychol Compass*. 2008;2(1):302–17.
14. Langeslag SJE, Schmidt M, Ghassabian A, Jaddoe VW, Hofman A, van der Lugt A, et al. Functional connectivity between parietal and frontal brain regions and intelligence in young children: the

- Generation R study. *Hum Brain Mapp*. 2013 Dec;34(12):3299–307.
15. Zapala MA, Schork NJ. Statistical Properties of Multivariate Distance Matrix Regression for High-Dimensional Data Analysis. *Front Genet* [Internet]. 2012 [cited 2018 Aug 27];3. Available from: <http://journal.frontiersin.org/article/10.3389/fgene.2012.00190/abstract>
 16. McArtor DB, Lubke GH, Bergeman CS. Extending multivariate distance matrix regression with an effect size measure and the asymptotic null distribution of the test statistic. *Psychometrika*. 2017 Dec;82(4):1052–77.
 17. Mullen EM. Mullen scales of early learning. AGS Circle Pines, MN; 1995.
 18. Beran TN, Elliott, C. D. (2007). *Differential Ability Scales* (2nd ed.). San Antonio, TX: Harcourt Assessment. *Can J Sch Psychol*. 2007 Jun;22(1):128–32.
 19. Gotham K, Pickles A, Lord C. Standardizing ADOS Scores for a Measure of Severity in Autism Spectrum Disorders. *J Autism Dev Disord*. 2009 May;39(5):693–705.
 20. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord*. 1994 Oct;24(5):659–85.
 21. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The Autism Diagnostic Observation Schedule–Generic: A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. 2000;30(3):205–23.
 22. Lord C, Rutter M, DiLavore PC, Risi, Gotham K, Bishop S. *Autism Diagnostic Observation Schedule*. 2nd ed. Torrance, CA: Western Psychological Services; 2012.
 23. Masyn KE. Latent class analysis and finite mixture modeling. In: *The Oxford handbook of quantitative methods: Statistical analysis*, Vol 2. New York, NY, US: Oxford University Press; 2013. p. 551–611. (Oxford library of psychology).
 24. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Contr*. 1974;19.
 25. Schwarz G. Estimating the Dimension of a Model. *Ann Stat*. 1978;6(2):461–4.
 26. Sclove SL. Application of model-selection criteria to some problems in multivariate analysis. *Psychometrika*. 1987 Sep;52(3):333–43.
 27. Diccicco TJ, Kass RE, Raftery A, Wasserman L. Computing Bayes Factors by Combining Simulation and Asymptotic Approximations. *J Am Stat Assoc*. 1997 Sep 1;92(439):903–15.
 28. Wasserman L. Bayesian Model Selection and Model Averaging. *J Math Psychol*. 2000 Mar 1;44(1):92–107.
 29. Nordahl CW, Simon TJ, Zierhut C, Solomon M, Rogers SJ, Amaral DG. Brief Report: Methods for Acquiring Structural MRI Data in Very Young Children with Autism Without the Use of Sedation. *J Autism Dev Disord*. 2008 Sep;38(8):1581–90.
 30. Nordahl CW, Scholz R, Yang X, Buonocore MH, Simon T, Rogers S, et al. Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study. *Arch Gen Psychiatry*. 2012 Jan;69(1):53–61.

31. Nordahl CW, Mello M, Shen AM, Shen MD, Vismara LA, Li D, et al. Methods for acquiring MRI data in children with autism spectrum disorder and intellectual impairment without the use of sedation. *J Neurodev Disord*. 2016 May 5;8(1):20.
32. Mori S, Wu D, Ceritoglu C, Li Y, Kolasny A, Vaillant MA, et al. MRICloud: Delivering High-Throughput MRI Neuroinformatics as Cloud-Based Software as a Service. *Comput Sci Eng*. 2016 Sep;18(5):21–35.
33. Oishi K, Faria A, Jiang H, Li X, Akhter K, Zhang J, et al. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. *Neuroimage*. 2009;46(2):486–99.
34. Shattuck DW, Mirza M, Adisetiyo V, Hojatkashani C, Salamon G, Narr KL, et al. Construction of a 3D probabilistic atlas of human cortical structures. *NeuroImage*. 2008 Feb 1;39(3):1064–80.
35. Ceritoglu C, Oishi K, Li X, Chou MC, Younes L, Albert M, et al. Multi-contrast large deformation diffeomorphic metric mapping for diffusion tensor imaging. *Neuroimage*. 2009;47(2):618–27.
36. Tang X, Oishi K, Faria AV, Hillis AE, Albert MS, Mori S, et al. Bayesian Parameter Estimation and Segmentation in the Multi-Atlas Random Orbit Model. Rapallo F, editor. *PLoS ONE*. 2013 Jun;8(6):e65591–e65591.
37. Wang H, Yushkevich PA. Multi-atlas segmentation with joint label fusion and corrective learning—an open source implementation. *Front Neuroinformatics* [Internet]. 2013 Nov 22 [cited 2018 Nov 8];7. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3837555/>
38. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A*. 2009 Aug;106(31):13040–5.
39. Lee JK, Amaral DG, Solomon M, Rogers SJ, Ozonoff S, Nordahl CW. Sex Differences in the Amygdala Resting-State Connectome of Children With Autism Spectrum Disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2020;5(3):320–9.
40. Satterthwaite TD, Vandekar SN, Wolf DH, Bassett DS, Ruparel K, Shehzad Z, et al. Connectome-wide network analysis of youth with Psychosis-Spectrum symptoms. *Mol Psychiatry*. 2015 Dec;20(12):1508–15.
41. Gower JC. Some Distance Properties of Latent Root and Vector Methods Used in Multivariate Analysis. 1966;53(3/4):325–38.
42. Aggarwal CC, Hinneburg A, Keim DA. On the Surprising Behavior of Distance Metrics in High Dimensional Space. In: Van den Bussche J, Vianu V, editors. *Database Theory — ICDT 2001*. Berlin, Heidelberg: Springer; 2001. p. 420–34. (Lecture Notes in Computer Science).
43. Anderson MJ, Willis TJ. Canonical Analysis of Principal Coordinates: A Useful Method of Constrained Ordination for Ecology. *Ecology*. 2003;84(2):511–25.
44. Legendre P, Anderson MJ. Distance-Based Redundancy Analysis: Testing Multispecies Responses in Multifactorial Ecological Experiments. *Ecol Monogr*. 1999;69(1):1–24.

45. Apostol TM, Mnatsakanian MA. Sums of Squares of Distances in m-Space. Am Math Mon. 2003 Jun 1;110(6):516–26.
46. Song M, Zhou Y, Li J, Liu Y, Tian L, Yu C, et al. Brain spontaneous functional connectivity and intelligence. NeuroImage. 2008 Jul 1;41(3):1168–76.
47. Harrison BJ, Pujol J, López-Solà M, Hernández-Ribas R, Deus J, Ortiz H, et al. Consistency and functional specialization in the default mode brain network. Proc Natl Acad Sci. 2008 Jul 15;105(28):9781–6.
48. Hearne LJ, Mattingley JB, Cocchi L. Functional brain networks related to individual differences in human intelligence at rest. Sci Rep. 2016 Aug 26;6:32328.
49. Cañete-Massé C, Carbó-Carreté M, Però-Cebollero M, Guàrdia-Olmos J. Task-Related Brain Connectivity Activation Functional Magnetic Resonance Imaging in Intellectual Disability Population: A Meta-analytic Study. Brain Connect [Internet]. 2021 Mar 24 [cited 2021 Oct 26]; Available from: <https://www.liebertpub.com/doi/full/10.1089/brain.2020.0911>
50. Vega JN, Hohman TJ, Pryweller JR, Dykens EM, Thornton-Wells TA. Resting-State Functional Connectivity in Individuals with Down Syndrome and Williams Syndrome Compared with Typically Developing Controls. Brain Connect. 2015 Oct 1;5(8):461–75.
51. Ma X, Tan J, Jiang L, Wang X, Cheng B, Xie P, et al. Aberrant Structural and Functional Developmental Trajectories in Children With Intellectual Disability. Front Psychiatry. 2021;12:53.
52. Dryburgh E, McKenna S, Rekik I. Predicting full-scale and verbal intelligence scores from functional Connectomic data in individuals with autism Spectrum disorder. Brain Imaging Behav. 2020 Oct 1;14(5):1769–78.
53. Pua EPK, Malpas CB, Bowden SC, Seal ML. Different brain networks underlying intelligence in Autism Spectrum Disorders [Internet]. 2018 Jun [cited 2021 Oct 27] p. 143891. Available from: <https://www.biorxiv.org/content/10.1101/143891v2>
54. Doshi-Velez F, Ge Y, Kohane I. Comorbidity Clusters in Autism Spectrum Disorders: An Electronic Health Record Time-Series Analysis. Pediatrics. 2014 Jan 1;133(1):e54–63.
55. Kim SH, Macari S, Koller J, Chawarska K. Examining the phenotypic heterogeneity of early autism spectrum disorder: subtypes and short-term outcomes. J Child Psychol Psychiatry. 2016;57(1):93–102.
56. Lai M-C, Kasseh C, Besney R, Bonato S, Hull L, Mandy W, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. Lancet Psychiatry. 2019 Oct 1;6(10):819–29.
57. Solomon, M. (2021, September). *IQ phenotypes of autistic youth from early childhood to preadolescence*. Virtual keynote presentation at the Society for the Study of Behavioural Phenotypes (SSBP) Conference.
58. Doshi-Velez, F., Ge, Y., & Kohane, I. (2014). Comorbidity clusters in autism spectrum disorders: an electronic health record time-series analysis. *Pediatrics*, 133(1), e54-e63.

59. Tye, C., Runicles, A. K., Whitehouse, A. J., & Alvares, G. A. (2019). Characterizing the interplay between autism spectrum disorder and comorbid medical conditions: An integrative review. *Frontiers in Psychiatry, 9*, 751.
60. Kim, S. H., Macari, S., Koller, J., & Chawarska, K. (2016). Examining the phenotypic heterogeneity of early autism spectrum disorder: Subtypes and short-term outcomes. *Journal of Child Psychology and Psychiatry, 57*(1), 93–102.
61. Lai, M. C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., ... Ameis, S. H.(2019). Prevalence of co-occurring mental health diagnoses in the autism population:A systematic review and meta-analysis. *The Lancet Psychiatry, 6*(10), 819-829.
62. Xie, S., Karlsson, H., Dalman, C., Widman, L., Rai, D., Gardner, R. M., ... Lee, B.K. (2020). The familial risk of Autism Spectrum disorder with and without intellectual disability. *Autism Research, 13*(12), 2242-2250.

Tables

Table 1. Sample Characteristics of Autistic Cohort

	Persistent High (n = 48)		Persistent Low (n = 108)		Changers (n = 109)	
	Males	Females	Males	Females	Males	Females
Participants	30	18	76	32	70	39
Baseline DQ/IQ	97.8 (12.3)	97.3 (11.8)	46.5 (10.7)	44.0 (12.7)	66.5 (11.1)	70.3 (11.1)
Outcome DQ/IQ	106.0 (16.9)	106.0 (15.7)	46.5 (12.4)	40.2 (13.8)	84.3 (18.5)	79.3 (15.9)
Baseline ADOS CSS	6.8 (2.0)	6.3 (1.7)	7.9 (1.7)	8.4 (1.3)	7.2 (1.6)	7.0 (1.3)
Baseline Total Brain Volume (cm³)	1,063 (68)	1,011 (90)	1,087 (103)	1,001 (112)	1,072 (93)	1,011 (121)

Notes: Means (SD) are reported; DQ/IQ Developmental /Intelligence Quotient; ADOS CSS = ADOS Calibrated Severity Score.

Table 2. Paired Comparisons from Multivariate Distance Matrix Regressions

Model	Effect	Statistic	p
Fronto-Parietal	Persistent High vs Persistent Low	0.008	0.009
	Persistent High vs Changers	0.008	0.010
	Changers vs Persistent Low	0.003	0.721
Default Mode	Persistent High vs Persistent Low	0.004	0.391
	Persistent High vs Changers	0.007	0.023
	Changers vs Persistent Low	0.008	0.017

Notes: Models covaried for sex and age at baseline.

Figures

Fronto-Parietal Network

Figure 1

Multivariate distance matrix regression (MDMR) results indicate significantly different fronto-parietal network (FPN) volumes by longitudinal IQ trajectory. Ordination plot depicting the MDMR results using distance-based redundancy analysis (dbRDA), depicting group differences at baseline in early childhood. dbRDA is a dimension reduction method which facilitates visualization of high dimensional data into two dimensions. The black dots depict median centroid locations of the Changers, Persistent-Low (P-Low), and Persistent-High (P-High) groups on the first two dbRDA axes. The ellipsoids indicate the standard

error of the locations of each group-centroid on those two axes. The first dbRDA axis (horizontal) was highly associated with concurrent IQ at baseline.

Figure 2

Effect-size analysis of fronto-parietal network (FPN) volumes for pair-wise differences between the Changers, Persistent-Low (P-Low), and Persistent-High (P-High) IQ trajectory groups. Compared to P-High, both P-Low and Changers differed primarily in left inferior temporal and middle occipital gyri, regions broadly implicated in supporting language, semantic knowledge, and sensory integration, including visual information and object recognition.

Default Mode Network

Figure 3

Multivariate distance matrix regression (MDMR) results indicate significantly different default mode network (DMN) volumes by longitudinal IQ trajectory. Ordination plot depicting the MDMR results using distance-based redundancy analysis (dbRDA), depicting group differences at baseline in early childhood. dbRDA is a dimension reduction method which facilitates visualization of high dimensional data into two dimensions. The black dots depict median centroid locations of the Changers, Persistent-Low (P-Low), and Persistent-High (P-High) groups on the first two dbRDA axes. The ellipsoids indicate the standard

error of the locations of each group-centroid on those two axes. Changers significantly differed from both P-Low and P-High groups; differences depicted primarily by the 1st dbRDA axis

Default Mode Network

Figure 4

Effect-size analysis of default mode network (DMN) volumes for pair-wise differences between the Changers, Persistent-Low (P-Low), and Persistent-High (P-High) IQ trajectory groups. Compared to Changers, P-Low differed primarily by bilateral middle temporal gyri, while P-High exhibited a more diffuse set of regional differences.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SIFigure1.jpg](#)