Dataset factors influencing age-related changes in brain structure and function in neurodevelopmental conditions

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Abstract

With brain structure and function undergoing complex changes throughout childhood and adolescence, age is a critical consideration in neuroimaging studies, particularly for those of individuals with neurodevelopmental conditions. However, despite the increasing use of large, consortium-based datasets to examine brain structure and function in neurotypical and neurodivergent populations, it is unclear whether age-related changes are consistent between datasets, and whether inconsistencies related to differences in sample characteristics, such as demographics and phenotypic features, exist. To address this, we built models of age-related changes of brain structure (cortical thickness and surface area; *N*=1,579) and function (resting-state functional connectivity strength; *N*=1,792) in two neurodiverse datasets: the Province of Ontario Neurodevelopmental network (POND) and the Healthy Brain Network (HBN). We examined whether deviations from these models differed between the datasets, and explored whether these deviations were associated with demographic and clinical variables. We found significant differences between the two datasets for measures of cortical surface area and functional connectivity strength throughout the brain. For cortical surface area, the patterns of differences were associated with intelligence, while for functional connectivity strength, positive associations were observed with head motion. Our findings highlight that patterns of age-related changes in the brain may be influenced by demographic and phenotypic characteristics, and thus future studies should consider these when examining or controlling forage effects in analyses.

Introduction

The brain's structure and function undergo complex and protracted changes throughout childhood and adolescence due to neurobiological processes such as synaptogenesis, myelination, and synaptic pruning (Grayson & Fair, 2017; Mills & Tamnes, 2020; Norbom et al., 2021). Neurodevelopmental differences, such as those associated with autism spectrum disorder (autism), attention-deficit/hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD), can further impact the presentation of age-related changes, particularly given the heterogeneity in etiology, biology, and behaviour (Bruin et al., 2020; Lombardo et al., 2019; Wolfers et al., 2019). As such, age is a critical consideration in neuroimaging studies of neurotypical and neurodivergent populations.

While many studies directly examine age-related effects, age is often treated as a nuisance covariate (Hyatt et al., 2020). With increasing awareness of the importance of replicability in neuroimaging studies (Poldrack et al., 2017), it is becoming more common to leverage multiple consortium-based datasets to examine brain structure and function in neurotypical and neurodivergent populations (Abrol et al., 2023; Grotzinger et al., 2023; Marek et al., 2022; Nicolaisen-Sobesky et al., 2022; Romer et al., 2019; Vandewouw et al., 2023). However, these datasets differ in composition in terms factors which may influence age-related effects, such as participants' demographics (e.g., age, sex and gender, race and ethnicity, socioeconomic status), diagnosis, co-occurring conditions, and other phenotypic variables. Thus, treating age in the same manner in datasets with differing characteristics may not be appropriate.

Studies have examined the consistency of age-related changes in brain structure and function across neurotypical cohorts (Cao et al., 2017; Herting et al., 2018; Madan & Kensinger, 2017; Mills et al., 2016; Morandini et al., 2021; Tamnes et al., 2017; Wang et al., 2021). For example, annual percentage changes in cortical thickness and surface area across childhood and adulthood have been shown to differ between four samples of typically developing individuals, with the precise patterns varying across lobes of the brain (Tamnes et al., 2017). White matter volume has also been shown to peak at different age ranges in different cohorts, with those from the United States showing

decreased volume across age compared to European samples (Mills et al., 2016). These findings have important implications for those which not only are directly examining age-related effects, but also those which treat age as a covariate, as controlling for age in the same manner does not consider these differences. Yet, no studies have examined whether these changes are consistent between cohorts of neurodivergent children, and if not, what factors may be contributing to the inconsistencies. This is particularly critical to investigate given the large variability in demographic and phenotypic characteristics of samples across different cohorts, even when the same diagnosis labels are studied. To this end, we examined age-related changes of brain structure (cortical thickness and surface area) and function (functional connectivity strength) in two datasets of neurodiverse children and adolescents, namely the Province of Ontario Neurodevelopmental network (POND) and the Healthy Brain Network (HBN). We first built dataset-specific developmental models and evaluated whether deviations from these models differed between the POND and HBN individuals, separately for males and females. Next, we explored whether the patterns of between-dataset differences were associated with demographic and phenotypic variables.

Methods

Participants

Neuroimaging and phenotype data were obtained from two independently collected datasets: the Province of Ontario Neurodevelopmental network (POND; exported April 2023), and the Healthy Brain Network (HBN; Release 9). For both datasets, participants who were between 5-19 years of age and who were either neurotypical or had diagnoses of autism, attention-deficit/hyperactivity disorder (ADHD), or obsessive-compulsive disorder (OCD) were selected. Structural magnetic resonance imaging (sMRI) data were available for 868 POND (255 ADHD, 377 autism, 75 OCD, 161 TD) and 1,505 HBN (1,100 ADHD, 162 autism, 36 OCD, 207 TD) participants and resting-state functional magnetic imaging (rs-fMRI) data were available for 864 POND (211 ADHD, 385 autism, 92 OCD, 185 TD) and 1,459 HBN (1,068 ADHD, 160 autism, 29 OCD, 202 TD) participants. Informed consent and/or assent was obtained from the participants and/or caregivers. The current study was approved by the institution's

research ethics board, and both consortia studies were approved by the appropriate boards.

Data acquisition

For both datasets, T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequences (sMRI data) and five minutes of resting-state data with an echo planar imaging (EPI) sequence (rs-fMRI data). The POND the rs-fMRI data were obtained as participants watched either a movie of their choosing or the naturalistic movie paradigm akin to a screensaver, *Inscapes* (Vanderwal et al., 2015), while HBN participants viewed a fixation cross. While HBN collected two five-minute resting-state acquisitions, only one was selected to be consistent with POND. Acquisition parameters for the sMRI and rs-fMRI protocols for each POND and HBN site are presented in **Supplemental Table 1**.

Biological sex was collected as part of both studies and used in the current analysis; insufficient data on gender was available at the time of export. Phenotypic measures of core and co-occurring differences for the diagnostic categories (see **Supplemental Table 2**), socioeconomic status, and race and ethnicity data were also available for both datasets and were used to characterize each sample. Socioeconomic status was determined using the caregiver highest level of education and annual household income. Race and ethnicity data were collected for both datasets according to each country's census guidelines. Due to low sample size, categories for both datasets were collapsed into minoritized race/ethnicity and white for statistical tests.

Image processing

The sMRI data were processed using the CIVET pipeline (version 2.1.0; (Ad-Dab'bagh et al., 2006)) on CBRAIN (Sherif et al., 2014) with the automatic quality control pipeline, details of which are described elsewhere (Hammill et al., 2021; Kushki et al., 2019, 2021). Of the remaining participants that passed quality control, propensity score matching (Rosenbaum & Rubin, 1985) was used to identify a smaller subset of participants to ensure the datasets showed no significant difference in median age or sex proportion (see (Vandewouw et al., 2023), for further details). Measures of cortical

thickness and surface area were extracted for 76 brain regions defined using the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Across both datasets, ComBat harmonization (Fortin et al., 2018; Johnson et al., 2007) was used to adjust all measures for site effects, followed by the regression of total gray matter volume, using subsampling (10,000 iterations, each selecting 63.2% of the sample) for both steps to increase robustness (Da-ano et al., 2020).

The rs-fMRI data preprocessing was performed using fMRIPrep (Esteban et al., 2019, 2020), and is described in detail elsewhere (Vandewouw et al., 2023). Participants were required to have at least 2/3 of their data within the recommended motion thresholds to pass quality control. Of the remaining participants, propensity score matching was used to identify a smaller subset of individuals for which there was not a statistically significant between-dataset differences in median age, sex proportion, and median head motion (Vandewouw et al., 2023). The Schaefer cortical (Schaefer et al., 2018) and Melbourne subcortical (Tian et al., 2020) atlases were used to define 232 brain regions, and pairwise Pearson correlations were computed between region-averaged time series to construct rs-fMRI connectomes. ComBat harmonization with subsampling (Da-ano et al., 2020; Fortin et al., 2018; Johnson et al., 2007) was used to adjust the connectivity values for site effects across both datasets. The resulting connectomes were thresholded with orthogonal minimum spanning trees to remove spurious connections (Dimitriadis et al., 2017), and the functional connectivity strength of each brain region was extracted.

Modeling age-related changes

Computational models relating age to the regional sMRI (area and thickness) and rs-fMRI (connectivity strength) measures were built using Bayesian linear regression (BLR; (Huertas et al., 2017)). Unlike traditional regression, BLR estimates the posterior probability of the regression coefficient, capturing the expected variation or uncertainty around the predicted age-related change; this enables the computation of a statistical *z*-score, or deviation score, that is similar to a residual but also considers the uncertainty around the prediction (Huertas et al., 2017; Rutherford et al., 2022). BLR is comparable but less computationally expensive than similar techniques such as Gaussian process

141 regression (Fraza et al., 2021; Huertas et al., 2017). We used the BLR implementation
142 from the Predictive Clinical Neuroscience toolkit (version 0.25;
143 https://pcntoolkit.readthedocs.io/en/latest) in Python (version 3.9), applying a B-spline
144 basis expansion of age with three evenly spaced knots to model non-linearities, using
145 warping to model normal and non-normal distributions in the brain measures, and using
146 the Powell method for optimization of the Bayesian hyper-parameters.

147 Dataset- and sex-specific models were built. To promote generalizability, 80% of
148 participants of a given subgroup were used to build a model, with 20% withheld for
149 testing. This procedure was repeated 10,000 times, each time with a different randomly
150 selected subset of participants. Deviation scores (*z*-scores) were calculated from a built
151 model under two test scenarios: the model built on 80% of a given subgroup was tested
152 on 1) the remaining 20% of participants from the same subgroup, and 2) all other
153 participants. **Figure 1** depicts an example of this process where the model is built using
154 80% of the female participants in POND and tested on the remaining 20% of female
155 participants from POND, 100% of male participants from POND, and 100% of the HBN
156 participants (male and female). The models were also used to predict the expected
157 brain measure at 7-, 11-, and 15-years of age (approximately the first, second, and third
158 age quartiles). Median predictions and deviation scores were computed across all
159 iterations. This procedure was performed with both the full samples and smaller,
160 matched subsamples.

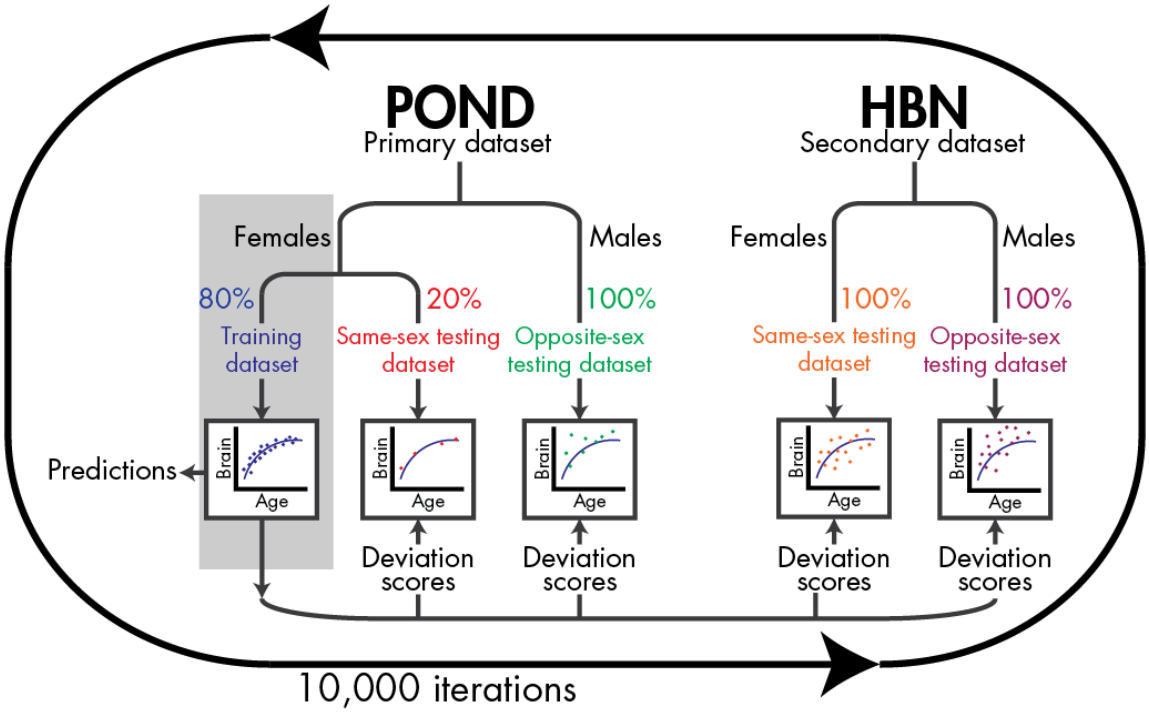

Figure 1: An example for the POND females of the subsampling approach for comparing the dataset- and sex-specific BLR models.

Statistics

First, differences between the two datasets in their demographic and clinical characteristics were examined, separately for males and females. Chi-squared tests, Kruskal-Wallis tests (given non-normality according to Shapiro-Wilks tests), and ordinal regressions were used for categorical, continuous, and ordinal variables, respectively, reporting Cramer's *v*, eta-squared, and odds ratio effect sizes; in all cases, significance was held at $p<0.05$.

For each of the brain measures, we compared the deviations between the primary (e.g., POND) and secondary (e.g., HBN) datasets; this was performed with both POND and HBN defined as the primary dataset, and separately for males and females. One-way ANOVAs or Kruskal-Wallis tests were used where appropriate, resulting *p*-values were adjusted using the false discovery rate (FDR) method, holding significance at $q<0.05$ and reporting eta-squared effect sizes. Results for the full and matched samples are presented in the main text and **Supplemental information**, respectively.

Given differences in demographic (socioeconomic status and race/ethnicity) and clinical (diagnosis and phenotypic measures) variables between POND and HBN, we explored what factors may be contributing to the between-dataset differences. To do so, for each brain measure, we extracted the deviations for each participant from their dataset- and sex-specific model and used generalized linear mixed-effects models to examine their associations with these variables; dataset and sex were modeled as random factors. Resulting *p*-values were FDR-corrected across the brain regions, and significance was held at $q < 0.05$.

Results

Participants

For the sMRI dataset, 754 HBN (214 female, 540 male) and 825 POND (270 female, 555 male) children and adolescents were included in the analysis; participant demographics are presented in **Table 1**, with phenotypic measures, socioeconomic status, and race/ethnicity for each dataset are presented in **Table 2**. Given the difference in age between the two datasets (females: $H(1)=104.35$, $p<.001$, $\eta^2=.04$; males: $H(1)=203.75$, $p<.001$, $\eta^2=.03$), a smaller, matched subset of participants was identified for which no significant difference remained, with each dataset consisting of 609 (178 females, 431 males) individuals (**Supplemental Table 3** and **4**).

Table 1: Participant demographics for the full sMRI sample.

			HBN	POND	Test-statistic [1]	*p*-value	Effect size
Female	***N***		214	270	–	–	–
	Dx (*N*)	**ADHD**	185	56	104.35	<.001	.46
		Autism	16	70			
		OCD	57	60			
		TD	12	28			
	Age[2] (years)		10.0 [8.1, 13.4]	12.0 [9.6, 15.0]	21.53	<.001	.04
Male	***N***		540	555	–	–	–
	Dx (*N*)	**ADHD**	399	167	203.75	<.001	.43
		Autism	74	245			
		OCD	69	86			
		TD	13	42			
	Age[2] (years)		10.2 [7.9, 13.1]	11.8 [9.6, 14.6]	38.30	<.001	.03

Note. HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; Dx: diagnosis; ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; TD: typically developing; [1]Kruskal-Wallis *H*-statistic for age with eta-squared effect size, and chi-squared statistic for diagnosis with Cramer's *v* effect size. [2]Age is reported as median [IQR].

Table 2: Socioeconomic status, race/ethnicity, and phenotypic measures for the full sMRI sample.

		HBN	POND	Test-statistic[1]	*p*-value	Effect size
Females	**Race/ethnicity[2]**					
	White	130	114	31.53	<.001	.28
	Other	119	27			
	Caregiver income[3]					
	<$50k/year	44	23			
	$50k-$150k	90	67	0.56	.578	1.12
	>$150k	86	44			
	Caregiver education[4]					
	< High school	9	1			
	High school	34	19	3.75	<.001	2.07
	College	87	88			
	Graduate	137	35			
	SCQ	6.0 [3.0, 9.0]	5.0 [2.0, 15.0]	0.06	.800	.02
	RBS-R	8.5 [2.0, 28.0]	10.0 [2.0, 28.0]	0.86	.353	.01
	SWAN-I	2.0 [0.0, 5.5]	2.0 [0.0, 6.0]	0.05	.823	<.01
	SWAN-HI	0.0 [0.0, 2.0]	1.0 [0.0, 3.0]	4.16	.041	.01
	TOCS	–	-5.0 [-39.5, 5.0]	–	–	–
	CBCL-OCS	2.0 [1.0, 5.0]	–	–	–	–
	FSIQ	102.0 [88.0, 114.5]	106.0 [94.0, 115.2]	3.31	.069	0.01
	CBCL-I	58.0 [48.0, 66.0]	61.5 [52.0, 69.0]	8.43	.004	0.02
	CBCL-E	56.0 [47.0, 65.0]	54.0 [44.0, 64.0]	1.71	.191	<.01
Males	**Race/ethnicity[2]**					
	White	255	224	49.25	<.001	.24
	Other	264	78			
	Caregiver income[3]					
	<$50k/year	81	61			
	$50k-$150k	170	150	3.41	.001	1.62
	>$150k	186	79			
	Caregiver education[4]					
	< High school	10	5			
	High school	97	45	4.04	<.001	1.70
	College	187	184			
	Graduate	251	75			
	SCQ	8.0 [5.0, 11.0]	10.0 [4.0, 20.0]	25.42	<.001	.07
	RBS-R	17.0 [4.0, 45.0]	16.0 [5.0, 31.0]	4.25	.039	<.01
	SWAN-I	3.0 [0.0, 6.0]	4.0 [1.0, 7.0]	7.48	.006	.01
	SWAN-HI	1.0 [0.0, 4.0]	2.0 [0.0, 6.0]	14.65	<.001	.01
	TOCS	–	-15.0 [-45.0, 2.0]	–	–	–
	CBCL-OCS	2.0 [1.0, 5.0]	–	–	–	–
	FSIQ	101.0 [86.0, 111.0]	100.0 [88.2, 111.0]	0.00	.945	<.01
	CBCL-I	58.0 [50.0, 67.0]	61.0 [52.0, 68.0]	10.25	.001	.01
	CBCL-E	57.0 [48.0, 66.0]	56.0 [46.0, 65.0]	2.21	.137	<.01

sMRI: structural magnetic resonance imaging; HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; SCQ: social communication questionnaire; RBS-R: repetitive Behaviours Scale – Revised; SWAN-I: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour inattention subscale; SWAN-HI: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour hyperactivity/impulsivity subscale; TOCS: Toronto Obsessive-Compulsive Scale; CBCL-OCS: Child Behaviour Checklist obsessive-compulsive subscale; FSIQ: full-scale intelligence quotient; CBCL-I: Child Behaviour Checklist internalizing problems subscale; CBCL-E: Child Behaviour Checklist externalizing problems subscale; [1]Kruskal-Wallis *H*-statistic for the non-normally distributed continuous variables with eta-squared effect sizes, chi-squared statistic for race/ethnicity with Cramer's *v* effect size, and ordinal regression with odds ratios for the ordinal variables; [2]Collected according to the respective country's census guidelines; [3]In the respective country's currency; [4]Collect includes associate and bachelor's degrees

For the fMRI dataset, 1072 HBN (349 females, 723 males) and 720 POND (207 females, 513 males) participants were included in the analysis (**Table 3**); phenotypic measures, socioeconomic status, and race/ethnicity for each dataset are shown in **Tables 4**. Significant between-dataset differences in age (females: $H(1)=21.34$, $p<.001$, $\eta^2=.04$; males: $H(1)=40.82$, $p<.001$, $\eta^2=.03$) and motion (females: $H(1)=36.50$, $p<.001$, $\eta^2=.03$; males: $H(1)=29.50$, $p<.001$, $\eta^2=.01$) were observed. Thus, a smaller, matched subset of children and adolescents with no such differences was identified, with each dataset consisting of 627 (189 female, 438 male) individuals (**Supplemental Table 5** and **6**).

Table 3: Participant demographics for the full fMRI sample.

			HBN	POND	Test-Statistic[1]	*p*-value	Effect size
Females	***N***		349	207	–	–	–
	Dx (*N*)	**ADHD**	232	39	142.43	<.001	.51
		Autism	24	71			
		OCD	13	31			
		TD	80	66			
	Age[2] (years)		10.2 [8.5, 13.1]	12.0 [9.5, 14.8]	21.34	<.001	.04
	Motion[2] (mm)		0.2 [0.1, 0.3]	0.1 [0.1, 0.2]	36.50	<.001	.03
Males	***N***		723	5135	–	–	–
	Dx (*N*)	**ADHD**	528	135	290.41	<.001	.48
		Autism	99	235			
		OCD	12	57			
		TD	84	86			
	Age[2] (years)		10.6 [8.6, 13.0]	12.1 [9.8, 14.9]	40.82	<.001	.03
	Motion[2] (mm)		0.2 [0.1, 0.3]	0.2 [0.1, 0.3]	29.50	<.001	.01

HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; TD: typically developing; [1]Kruskal-Wallis *H*-statistic for age with eta-squared effect size, and chi-squared statistic for diagnosis with Cramer's *v* effect size; [2]Age and motion is reported as median [IQR].

Table 4: Socioeconomic status, race/ethnicity, and phenotypic measures for the full fMRI sample.

		HBN	POND	Test-statistic[1]	*p*-value	Effect size
Females	**Race/ethnicity[2]**					
	White	175	112	30.81	<.001	.26
	Other	153	27			
	Caregiver income[3]					
	<$50k/year	55	24			
	$50k-$150k	117	67	0.69	.489	1.14
	>$150k	136	57			
	Caregiver education[4]					
	< High school	7	1			
	High school	42	18	3.79	<.001	2.00
	College	113	86			
	Graduate	183	42			
	SCQ	5.5 [3.0, 9.0]	5.0 [2.0, 15.0]	0.08	.782	.03
	RBS-R	8.0 [2.0, 27.5]	9.5 [2.0, 28.0]	0.59	.441	.01
	SWAN-I	2.0 [0.0, 6.0]	2.0 [0.0, 6.0]	0.15	.694	<.01
	SWAN-HI	0.0 [0.0, 2.0]	1.0 [0.0, 3.0]	4.53	.033	.01
	TOCS	–	-6.0 [-40.0, 6.0]	–	–	–
	CBCL-OCS	2.0 [1.0, 4.0]	–	–	–	–
	FSIQ	102.0 [90.5, 113.0]	106.0 [94.0, 115.0]	3.03	.082	<.01
	CBCL-I	56.0 [48.0, 65.2]	62.0 [52.0, 70.0]	15.17	<.001	.03
	CBCL-E	55.0 [47.0, 64.0]	54.0 [44.0, 63.0]	2.41	.121	.01
Males	**Race/ethnicity[2]**					
	White	332	223	59.40	<.001	.25
	Other	352	74			
	Caregiver income[3]					
	<$50k/year	123	53			
	$50k-$150k	240	143	1.27	.205	1.18
	>$150k	276	110			
	Caregiver education[4]					
	< High school	15	5			
	High school	125	44	3.52	<.001	1.55
	College	243	175			
	Graduate	329	84			
	SCQ	7.0 [4.0, 11.0]	9.0 [3.2, 19.0]	23.86	<.001	.06
	RBS-R	15.0 [3.0, 45.0]	15.0 [5.0, 28.0]	3.78	.052	.01
	SWAN-I	3.0 [0.0, 6.0]	4.0 [1.0, 7.0]	7.23	.007	.01
	SWAN-HI	1.0 [0.0, 3.0]	2.0 [0.0, 5.0]	30.42	<.001	.03
	TOCS	–	-14.5 [-45.0, 2.0]	–	–	–
	CBCL-OCS	2.0 [1.0, 4.0]	–	–	–	–
	FSIQ	100.0 [87.0, 110.0]	102.0 [89.8, 112.0]	1.35	.245	<.01
	CBCL-I	58.0 [50.0, 66.0]	61.0 [52.0, 68.0]	11.50	.001	.01
	CBCL-E	55.0 [48.0, 64.0]	55.0 [46.0, 65.0]	0.05	.820	<.01

fMRI: functional magnetic resonance imaging; HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; SCQ: social communication questionnaire; RBS-R: repetitive Behaviours Scale – Revised; SWAN-I: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour inattention subscale; SWAN-HI: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour hyperactivity/impulsivity subscale; TOCS: Toronto Obsessive-Compulsive Scale; CBCL-OCS: Child Behaviour Checklist obsessive-compulsive subscale; FSIQ: full-scale intelligence quotient; CBCL-I: Child Behaviour Checklist internalizing problems subscale; CBCL-E: Child Behaviour Checklist externalizing problems subscale; [1]Kruskal-Wallis *H*-statistic for the non-normally distributed continuous variables with eta-squared effect sizes, chi-squared statistic for race/ethnicity with Cramer's *v* effect size, and ordinal regression with odds ratios for the ordinal variables; [2]Collected according to the respective country's census guidelines; [3]In the respective country's currency; [4]Collect includes associate and bachelor's degrees

202 ***Dataset differences in deviations***

203 The deviation scores for the age models were compared between datasets,
204 separately for the males and females, with significant differences presented in **Figure 2**
205 for the full samples, and **Supplemental Figure 1** for the matched samples. To explore
206 what factors may be contributing to the observed differences, associations between
207 deviations and the demographic variables (age, sex, race/ethnicity, caregiver highest
208 level of education, and annual household income) and phenotypic variables (social
209 communication difficulties, repetitive behaviours, inattention, hyperactivity/impulsivity,
210 obsessive-compulsive traits, intelligence, internalizing problems, and externalizing
211 problems) were investigated.

212 For cortical surface area (**Figure 2A** and **Supplemental Figure 1A**), deviation
213 scores differed between the datasets throughout the brain, with consistent findings
214 between the full and matched samples. When examining the median deviation scores
215 for the significant regions, deviations for the POND participants were negative when the
216 models were built using the HBN participants, indicating that the HBN models
217 overestimated surface area for the POND individuals; on the other hand, POND models
218 underestimated surface area in the HBN participants (positive deviation scores). In both
219 the full and matched samples, significant positive associations between deviations and
220 intelligence were observed (**Supplemental Figure 2A**); all other associations were
221 insignificant (**Supplemental Table 7**).

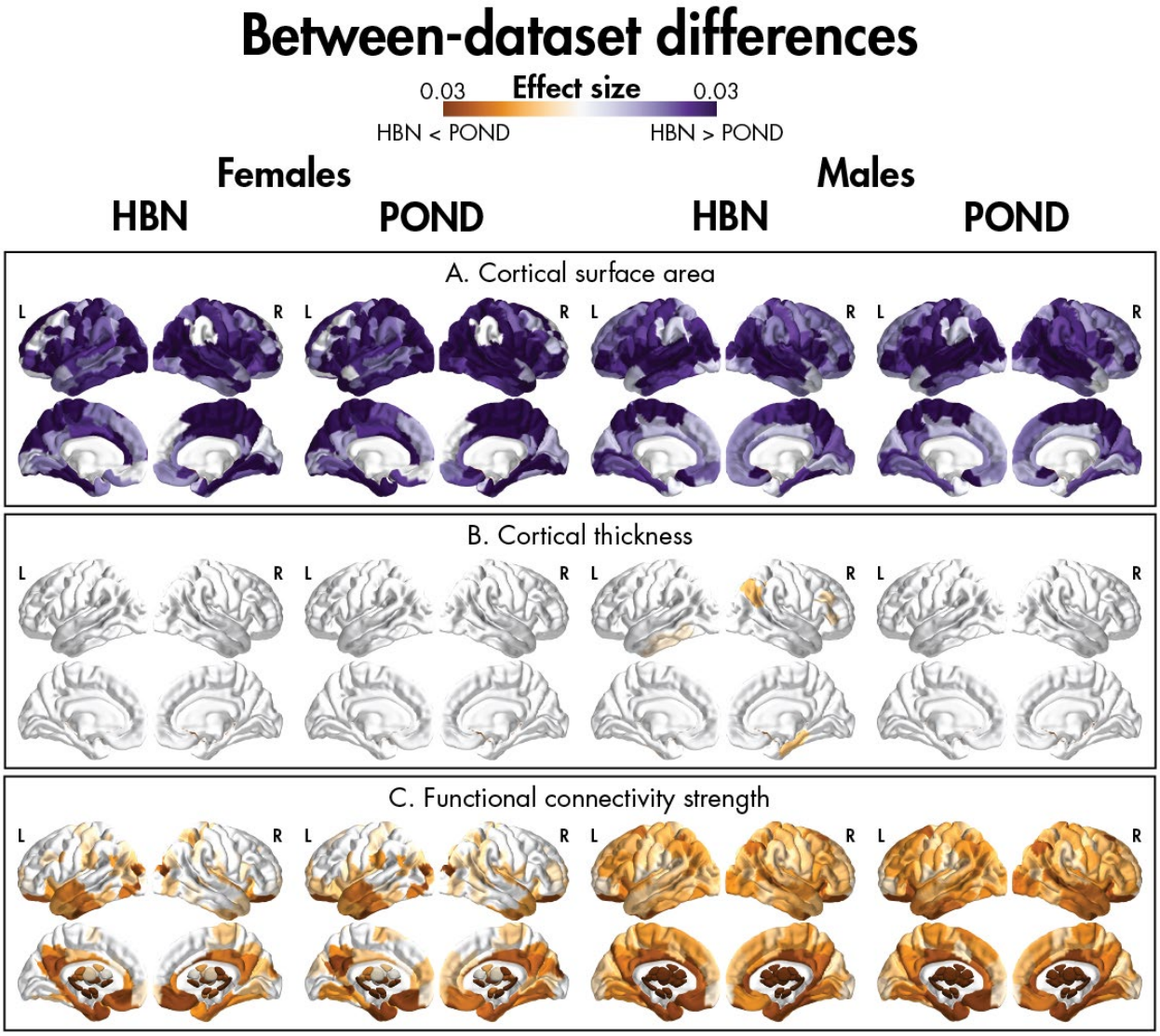

Figure 2: Effect sizes (eta-squared) for significant between-dataset differences in deviations from age-related models for the females (left) and males (right) from the full sample when the models were built using each dataset (HBN: Healthy Brain Network, POND: Province of Ontario Neurodevelopmental network).

For cortical thickness, few regions showed significant between-dataset differences in the deviation scores in the full sample (**Figure 2B**), with no regions showing significant effects in the matched sample (**Supplemental Figure 1B**).

For functional connectivity strength (**Figure 2C**; **Supplemental Figure 1C**), significant differences in the deviation scores between POND and HBN were observed throughout the brain, with more widespread effects observed in the males (HBN: 232 regions, POND: 232 regions) compared to females (HBN: 137 regions, POND: 151 regions). When models were built using the HBN individuals, median deviation scores

230 indicated that they underestimated functional connectivity strength in POND;
231 conversely, POND models overestimated connectivity strength in the HBN participants.
232 Deviation scores were significantly positively correlated with head motion
233 (**Supplemental Figure 2B**; **Supplemental Table 8**).

234 **Discussion**

235 In this study, using data from two consortia, namely POND and HBN, we built
236 dataset-specific models that describe age-related changes in measures of brain
237 structure and function. We determined that deviations from the models were
238 significantly different between the two datasets for measures of cortical surface area
239 and functional connectivity strength throughout the brain, but not cortical thickness;
240 these differences were observed within both males and females. For cortical surface
241 area, the patterns of differences were associated intelligence, suggesting that it may be
242 contributing to the between-dataset findings. On the other hand, for functional
243 connectivity strength, positive associations were observed with head motion.

244 Overall, our findings highlight that patterns of age-related changes in the brain
245 may not be consistent between cohorts of neurodiverse individuals, and these
246 inconsistencies may be related to differences in the demographic and phenotypic
247 composition of the sample. While previous work has identified factors such as
248 methodology and medication (Bednarz & Kana, 2018) as contributors to the lack of
249 convergence in the literature on the nature and directionality of brain differences in
250 neurodevelopmental conditions, we hypothesize that differences in age-related changes
251 between cohorts, potentially driven by differences in measures like intelligence and
252 head motion, are also contributing to the lack of consistent findings. Even though age
253 may not be the focus of a particular study, adjusting for age in the same manner in
254 multiple cohorts despite the presence of cohort-specific age-related effects can produce
255 downstream effects in subsequent analyses.

256 For cortical surface area, differences in deviations from age models differed
257 between POND and HBN throughout the brain, irrespective of which group was used to
258 construct the model. Deviations from age models of cortical surface area were also
259 shown to be positively associated with cortical surface area. The association between

cortical surface area and intelligence is well established (Lett et al., 2020; Schnack et al., 2015; Tadayon et al., 2020; Yang et al., 2023), with indication that intelligence is associated with both the magnitude and timing of cortical surface area development (Schnack et al., 2015).

While between-dataset differences in deviations from age models were observed for cortical surface area, this finding did not extend to cortical thickness. The development of cortical thickness and surface area are driven by different genetic and biological processes and show distinct maturational trajectories (Geschwind & Rakic, 2013; Panizzon et al., 2009; Tamnes et al., 2017; Vijayakumar et al., 2016; Wierenga et al., 2014). Surface area has also been shown to relate to general psychopathology, while this association is not observed with cortical thickness (Jalbrzikowski et al., 2019; Mewton et al., 2022; Romer et al., 2023; Schmaal et al., 2016), and the genetic association between brain volume and intelligence is driven by surface area and not thickness (Vuoksimaa et al., 2015). Thus, given the differences between POND and HBN in the core and co-occurring domains of neurodevelopmental conditions, we hypothesize that the unique relationship between psychopathology and intelligence with surface area is why differences in deviations are restricted to this structural measure rather than cortical thickness.

We also observed differences between POND and HBN in deviations from models describing changes in functional connectivity strength with age. Deviations from the models of age-related effects were also shown to be positively associated with head motion. Head motion is known to increase functional connectivity (Satterthwaite et al., 2013), and head motion is different between POND and HBN, possibly due to the use of a fixation-cross resting-state compared to movie paradigms (Vanderwal et al., 2015). Thus, we suggest that head motion may be driving deviations in age-related changes of functional connectivity; this conclusion is supported by decreased effect sizes in the motion-matched subsample, although this is only observed in the males.

The results of this study should be interpreted considering several limitations. This study is cross-sectional, and future studies should leverage longitudinal data to validate our developmental findings. We also only constructed age models that were

specific to a binarized measure of biological sex; future work should also examine gender-specific patterns. Finally, given the sample size required to establish reproducible brain-behaviour associations (Marek et al., 2022), the contribution of the identified factors to deviations from age models should be validated in larger samples.

The replicability crisis has posed a significant challenge to the neuroscience field and to the broader scientific community. In this context, we have questioned the extent to which age-related changes of brain structure and function are consistent between two independent cohorts of individuals with neurodevelopmental conditions. While deriving the neurobiological changes that occur during development is often a specific research goal, the presence or absence of replicable developmental effects is also highly relevant for all investigations which include age at any step in the methodology. Given our findings that age-related differences are not consistent across phenotypic and acquisition variables, these need to be considered as covariates when examining, or correcting, for age.

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Supplemental information

Supplemental Table 1: Acquisition parameters for the sMRI and rs-fMRI protocols for each site in the POND and HBN datasets.

Dataset	Scanner	Scan type	Sequence	TR (ms)	TE (ms)	FA (°)	FOV (mm)	Voxel size (mm)	Scan time (min)
sMRI protocol									
	SK: 3T TimTrio	–	MPRAGE	2300	2.96	9	192×240×256	1	5.0
	QU: 3T TimTrio	–	MPRAGE	2300	3.14	9	192×240×256	0.8	6.2
	SK: 3T Prisma^{fit}	–	MPRAGE	1870	3.14	9	192×240×256	0.8	5.0
	QU: 3T Prisma^{fit}	–	MPRAGE	1870	3.10	9	192×240×256	0.8	5.0
POND	HB: 3T Prisma^{fit}	–	MPRAGE	1870	3.10	9	192×240×256	0.8	5.0
	CBIC: 3T Prisma^{fit}	–	MPRAGE	2500	3.15	8	179×256×256	0.8	7.00
	CUNY: 3T Prisma^{fit}	–	MPRAGE	2500	3.15	8	179×256×256	0.8	7.00
	RU: 3T TimTrio	–	MPRAGE	2500	3.15	8	179×256×256	0.8	7.00
HBN	SI: 1.5T Avanto	–	MPRAGE	2730	1.64	7	176×256×256	1	6.53
fMRI protocol									
	SK: 3T TimTrio	Movies	EPI	2340	30	70	224×224×140	3.5	5.1
	QU: 3T TimTrio	Inscapes	EPI	2340	30	70	224×224×140	3.5	5.1
	SK: 3T Prisma^{fit}	Inscapes	EPI	1500	30	70	222×222×150	3.0	5.1
	QU: 3T Prisma^{fit}	Inscapes	EPI	1500	30	70	222×222×150	3.0	5.1
POND	HB: 3T Prisma^{fit}	Inscapes	EPI	1500	30	70	222×222×150	3.0	5.1
	CBIC: 3T Prisma^{fit}	Fixation	EPI	800	30	31	202×202×144	2.4	2×5.1
	CUNY: 3T Prisma^{fit}	Fixation	EPI	800	30	31	202×202×144	2.4	2×5.1
	RU: 3T TimTrio	Fixation	EPI	800	30	31	202×202×144	2.4	2×5.1
	SI: 1.5T Avanto	Fixation	EPI	1450	40	55	195×195×135	2.5	10.3
	SK: 3T TimTrio	Movies	EPI	2340	30	70	224×224×140	3.5	5.0
HBN	QU: 3T TimTrio	Inscapes	EPI	2340	30	70	224×224×140	3.5	5.0

sMRI: structural magnetic resonance imaging; rs-fMRI: resting-state functional magnetic resonance imaging; POND: Province of Ontario Neurodevelopmental network; HBN: Healthy Brain Network; SK: Hospital for Sick Children; QU: Queen's University; HB: Holland Bloorview Kids Rehabilitation Hospital; CBIC: CitiGroup Cornell Brain Imaging Center; CUNY: the City University of New York Advanced Science Research Center; RU: Rutgers University; SI: Staten Island; TR: repetition time; TE: echo time; FA: flip angle; FOV: field of view

Supplemental Table 2: Summary of the phenotypic measures of core and co-occurring differences for the diagnostic categories.

Domain	Assessment	Score	Range	Interpretation[1]	Acronym
Social communication difficulties	Social Communication Questionnaire (Rutter et al., 2003)	Total score	0-39	More severe difficulties with social communication	SCQ
Repetitive behaviours	Repetitive Behaviours Scale – Revised (Bodfish et al., 2000)	Total score	0-129	More severe repetitive behaviours	RBS-R
Inattention	Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour (Swanson et al., 2012)	Inattention subscale	0-9	More severe difficulties with inattention	SWAN-I
Hyperactivity	Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour (Swanson et al., 2012)	Hyperactivity subscale	0-9	More severe difficulties with hyperactivity/impulsivity	SWAN-HI
Obsessive-compulsive traits	Toronto Obsessive-Compulsive Scale (Nelson et al., 2001)	Total score	-63-63	More severe obsessive-compulsive traits	TOCS
	Child Behaviour Checklist (Nelson et al., 2001)	Obsessive-compulsive subscale	0-16	More severe obsessive-compulsive traits	CBCL-OCS
Intelligence	Age-appropriate Wechsler or Stanford-Binet scales	Full-scale intelligence quotient	40-160	Higher intelligence	FSIQ
Internalizing problems	Child Behaviour Checklist (Achenbach & Ruffle, 2000)	Internalizing problems subscale	40-75	Worse internalizing problems	CBCL-I
Externalizing problems	Child Behaviour Checklist (Achenbach & Ruffle, 2000)	Externalizing problems subscale	40-75	Worse externalizing problems	CBCL-E

[1]Interpretation: relative to higher scores

Supplemental Table 3: Participant demographics for the matched sMRI sample.

			HBN	POND	Test-Statistic[1]	*p*-value	Effect size
Females	*N*		178	178	–	–	–
	Dx (*N*)	ADHD	124	51	76.33	<.001	.46
		Autism	7	56			
		OCD	38	47			
		TD	9	27			
	Age[2] (years)		10.1 [8.5, 13.3]	11.1 [9.0, 13.3]	2.61	.107	<.01
Males	*N*		431	431	–	–	–
	Dx (*N*)	ADHD	304	145	141.73	<.001	.41
		Autism	55	190			
		OCD	61	63			
		TD	11	33			
	Age[2] (years)		10.6 [8.6, 13.0]	10.9 [9.0, 13.0]	2.07	.150	<.01

HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; TD: typically developing; [1]Kruskal-Wallis *H*-statistic for age with eta-squared effect size, and chi-squared statistic for diagnosis with Cramer's *v* effect size; [2]Age is reported as median [IQR].

Supplemental Table 4: Socioeconomic status, race/ethnicity, and phenotypic measures for the matched sMRI sample.

		HBN	POND	Test-Statistic[1]	*p*-value	Effect size
Females	Race/ethnicity[2]					
	White	86	92	21.18	<.001	.28
	Other	78	24			
	Caregiver income[3]					
	<$50k/year	31	18			
	$50k-$150k	65	57	0.03	.974	0.99
	>$150k	51	34			
	Caregiver education[4]					
	< High school	6	1			
	High school	19	15	3.88	<.001	2.44
	College	58	72			
	Graduate	94	27			
	SCQ	6.0 [4.0, 8.0]	5.0 [2.0, 14.2]	0.18	.675	.02
	RBS-R	11.0 [2.0, 28.0]	11.5 [2.0, 29.0]	0.22	.639	.01
	SWAN-I	2.0 [0.0, 5.0]	2.0 [0.0, 7.0]	0.04	.843	<.01
	SWAN-HI	0.0 [0.0, 2.0]	1.0 [0.0, 4.0]	7.16	.007	.02
	TOCS	–	-6.0 [-40.0, 6.0]	–	–	–
	CBCL-OCS	2.0 [1.0, 4.8]	–	–	–	–
	FSIQ	102.0 [87.0, 113.5]	106.0 [94.0, 115.0]	1.90	.168	.01
	CBCL-I	56.0 [48.0, 65.0]	60.0 [52.0, 69.0]	6.91	.009	.02
	CBCL-E	57.0 [47.0, 64.8]	55.0 [44.0, 64.0]	0.80	.372	<.01
Males	Race/ethnicity[2]					
	White	205	168	26.58	<.001	.20
	Other	202	68			
	Caregiver income[3]					
	<$50k/year	67	47			
	$50k-$150k	133	123	3.09	.002	1.64
	>$150k	146	58			
	Caregiver education[4]					
	< High school	6	4			
	High school	79	30	3.39	.001	1.66
	College	143	149			
	Graduate	196	57			
	SCQ	8.0 [5.0, 11.0]	10.0 [4.0, 20.0]	19.42	<.001	.06
	RBS-R	14.5 [4.0, 44.0]	16.0 [5.0, 31.0]	0.77	.381	<.01
	SWAN-I	3.0 [0.0, 6.0]	4.0 [1.0, 7.0]	11.37	<.001	.01
	SWAN-HI	1.0 [0.0, 4.0]	2.0 [0.0, 6.0]	22.60	<.001	.03
	TOCS	–	-15.0 [-45.0, 2.0]	–	–	–
	CBCL-OCS	2.0 [1.0, 5.0]	–	–	–	–
	FSIQ	100.5 [87.0, 111.0]	101.0 [88.0, 111.0]	0.07	.794	<.01
	CBCL-I	58.0 [50.0, 67.0]	62.0 [52.0, 68.0]	10.87	.001	.01
	CBCL-E	56.0 [48.0, 65.0]	56.0 [48.0, 66.0]	0.06	.814	<.01

sMRI: structural magnetic resonance imaging; HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; SCQ: social communication questionnaire; RBS-R: repetitive Behaviours Scale – Revised; SWAN-I: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour inattention subscale; SWAN-HI: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour hyperactivity/impulsivity subscale; TOCS: Toronto Obsessive-Compulsive Scale; CBCL-OCS: Child Behaviour Checklist obsessive-compulsive subscale; FSIQ: full-scale intelligence quotient; CBCL-I: Child Behaviour Checklist internalizing problems subscale; CBCL-E: Child Behaviour Checklist externalizing problems subscale; [1]Kruskal-Wallis *H*-statistic for the non-normally distributed continuous variables with eta-squared effect sizes, chi-squared statistic for race/ethnicity with Cramer's *v* effect size, and ordinal regression with odds ratios for the ordinal variables; [2]Collected according to the respective country's census guidelines; [3]In the respective country's currency; [4]Collect includes associate and bachelor's degrees

Supplemental Table 5: Participant demographics for the matched fMRI sample.

			HBN	POND	Test-Statistic[1]	*p*-value	Effect size
Females	*N*		189	189	–	–	–
	Dx (*N*)	ADHD	130	38	107.87	<.001	.53
		Autism	7	65			
		OCD	12	31			
		TD	40	55			
	Age[2] (years)		10.7 [8.7, 13.4]	11.7 [9.4, 14.0]	2.77	.096	.01
	Motion[2] (mm)		0.1 [0.1, 0.2]	0.1 [0.1, 0.2]	2.09	.148	<.01
Males	*N*		438	438	–	–	–
	Dx (*N*)	ADHD	321	121	202.91	<.001	.48
		Autism	53	192			
		OCD	7	48			
		TD	57	77			
	Age[2] (years)		10.9 [9.0, 13.1]	11.4 [9.4, 13.6]	2.75	.097	<.01
	Motion[2] (mm)		0.2 [0.1, 0.2]	0.2 [0.1, 0.3]	0.53	.466	<.01

HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; TD: typically developing; [1]Kruskal-Wallis *H*-statistic for age with eta-squared effect size, and chi-squared statistic for diagnosis with Cramer's *v* effect size; [2]Age and motion is reported as median [IQR].

Supplemental Table 6: Socioeconomic status, race/ethnicity, and phenotypic measures for the matched fMRI sample.

		HBN	POND	Test-statistic[1]	*p*-value	Effect size
Females	Race/ethnicity[2]					
	White	102	100	14.34	<.001	.22
	Other	74	27			
	Caregiver income[3]					
	<$50k/year	32	20	0.00	.999	1.00
	$50k-$150k	68	62			
	>$150k	71	52			
	Caregiver education[4]					
	< High school	2	1	4.04	<.001	2.45
	High school	16	16			
	College	69	77			
	Graduate	102	38			
	SCQ	5.0 [3.0, 8.5]	5.0 [2.0, 14.2]	0.01	.917	.03
	RBS-R	10.0 [2.0, 27.2]	11.0 [2.0, 29.0]	0.11	.741	.01
	SWAN-I	2.0 [0.0, 5.8]	2.0 [0.0, 6.0]	0.00	.987	<.01
	SWAN-HI	0.0 [0.0, 2.0]	1.0 [0.0, 3.0]	6.81	.009	.03
	TOCS	–	-5.0 [-39.8, 7.8]	–	–	–
	CBCL-OCS	2.0 [1.0, 5.0]	–	–	–	–
	FSIQ	104.0 [91.0, 116.0]	106.0 [94.0, 115.0]	0.37	.544	<.01
	CBCL-I	56.0 [48.0, 65.0]	62.0 [52.0, 70.0]	10.73	.001	.03
	CBCL-E	54.0 [47.0, 64.2]	54.0 [44.0, 64.0]	0.94	.333	<.01
Males	Race/ethnicity[2]					
	White	219	185	30.07	<.001	.21
	Other	202	67			
	Caregiver income[3]					
	<$50k/year	66	46	1.37	.171	1.23
	$50k-$150k	158	124			
	>$150k	169	97			
	Caregiver education[4]					
	< High school	5	4	3.24	.001	1.60
	High school	77	33			
	College	144	155			
	Graduate	205	73			
	SCQ	7.0 [4.0, 10.0]	9.0 [3.0, 18.5]	14.08	<.001	.06
	RBS-R	12.0 [2.0, 40.8]	15.0 [5.0, 27.0]	0.51	.474	<.01
	SWAN-I	3.0 [0.0, 6.0]	4.0 [1.0, 7.0]	5.85	.016	.01
	SWAN-HI	0.0 [0.0, 3.0]	2.0 [0.0, 6.0]	38.64	<.001	.05
	TOCS	–	-15.0 [-44.0, 2.0]	–	–	–
	CBCL-OCS	2.0 [1.0, 4.0]	–	–	–	–
	FSIQ	99.0 [86.0, 110.0]	101.0 [89.5, 111.5]	1.32	.250	<.01
	CBCL-I	58.0 [49.0, 67.0]	61.0 [52.0, 68.0]	8.84	.003	.01
	CBCL-E	54.0 [46.0, 63.0]	56.0 [46.0, 66.2]	1.97	.161	<.01

fMRI: functional magnetic resonance imaging; HBN: Healthy Brain Network; POND: Province of Ontario Neurodevelopmental network; SCQ: social communication questionnaire; RBS-R: repetitive Behaviours Scale – Revised; SWAN-I: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour inattention subscale; SWAN-HI: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour hyperactivity/impulsivity subscale; TOCS: Toronto Obsessive-Compulsive Scale; CBCL-OCS: Child Behaviour Checklist obsessive-compulsive subscale; FSIQ: full-scale intelligence quotient; CBCL-I: Child Behaviour Checklist internalizing problems subscale; CBCL-E: Child Behaviour Checklist externalizing problems subscale; [1]Kruskal-Wallis *H*-statistic for the non-normally distributed continuous variables with eta-squared effect sizes, chi-squared statistic for race/ethnicity with Cramer's *v* effect size, and ordinal regression with odds ratios for the ordinal variables; [2]Collected according to the respective country's census guidelines; [3]In the respective country's currency; [4]Collect includes associate and bachelor's degrees

Supplemental Table 7: Correlation between the effect sizes for the between-dataset difference in deviation scores and associations with demographic and clinical variables for cortical surface area in the full sample.

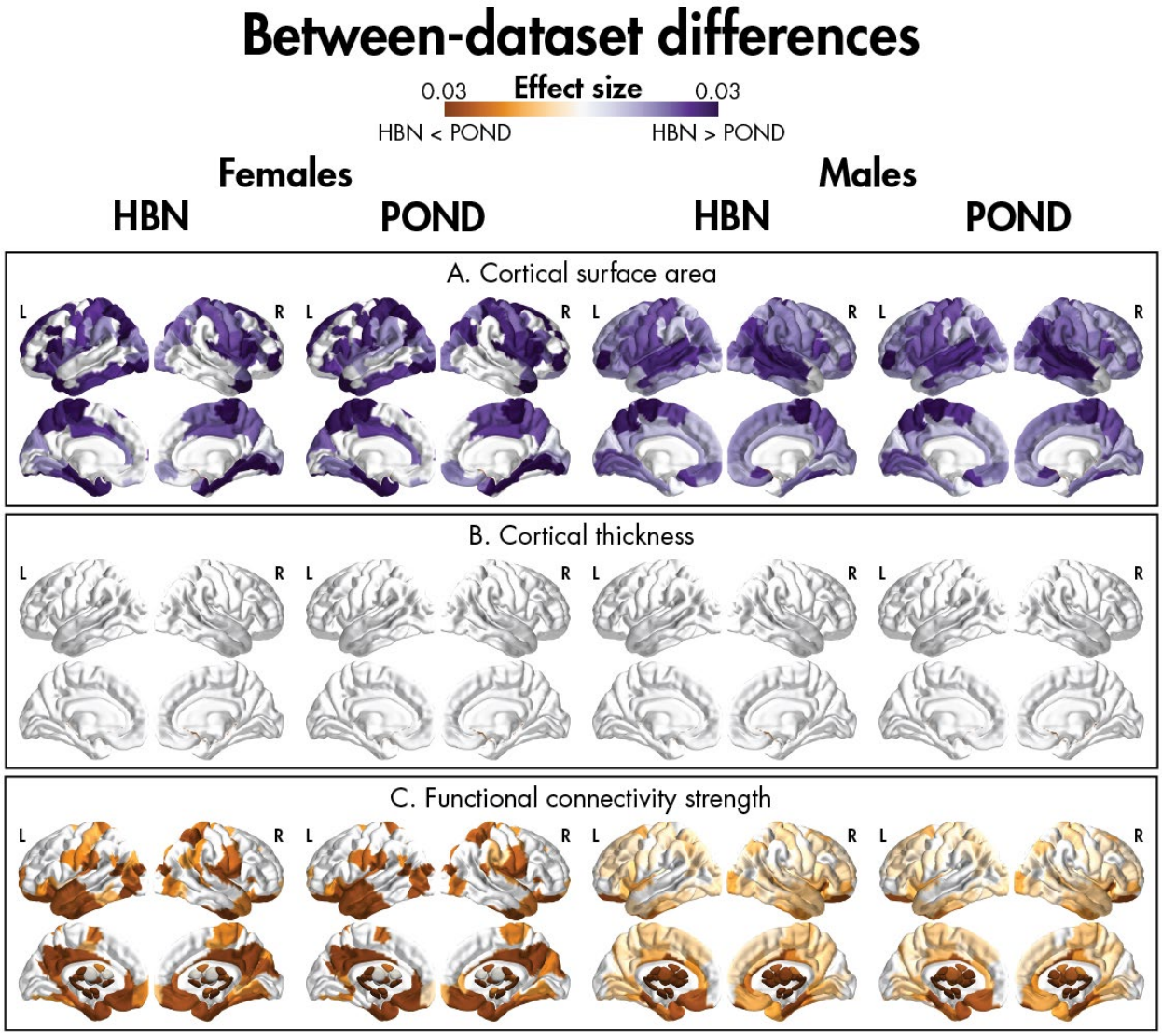
	Correlation value	*p*-value
Dx	.16	.007
Race/ethnicity	.02	.674
Caregiver income	.00	.975
Caregiver education	.07	.223
SCQ	.08	.155
RBS-R	-.05	.422
SWAN-I	.14	.014
SWAN-HI	<.01	.990
FSIQ	.21	<.001
CBCL-I	.03	.576
CBCL-E	.09	.101

SCQ: social communication questionnaire; RBS-R: repetitive Behaviours Scale – Revised; SWAN-I: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour inattention subscale; SWAN-HI: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour hyperactivity/impulsivity subscale; FSIQ: full-scale intelligence quotient; CBCL-I: Child Behaviour Checklist internalizing problems subscale; CBCL-E: Child Behaviour Checklist externalizing problems subscale

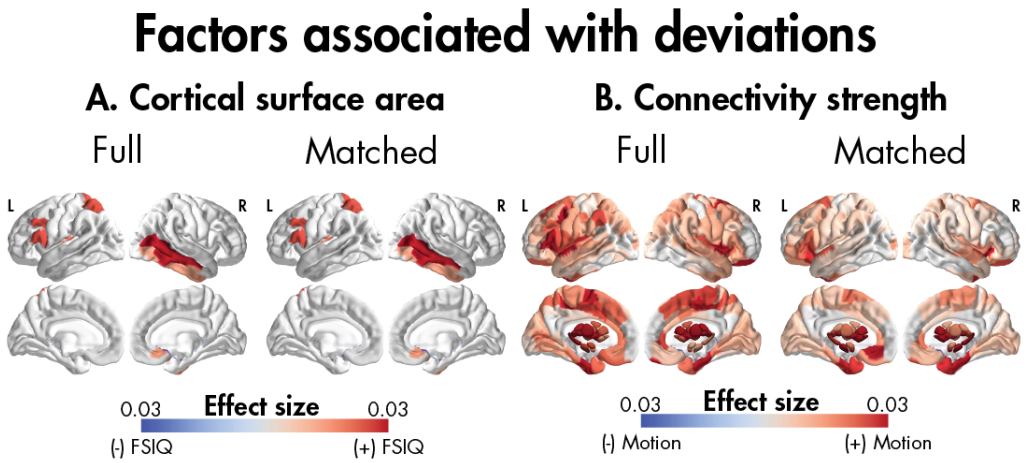
Supplemental Table 8: Correlation between the effect sizes for the between-dataset difference in deviation scores and associations with demographic and clinical variables for functional connectivity strength in the full sample.

	Correlation value	*p*-value
Dx	-.05	.127
Motion	.20	<.001
Race/ethnicity	-.18	<.001
Caregiver income	-.13	<.001
Caregiver education	-.03	.417
SCQ	-.01	.803
RBS-R	-.12	<.001
SWAN-I	.02	.576
SWAN-HI	.03	.352
FSIQ	-.06	.072
CBCL-I	-.06	.050
CBCL-E	-.06	.054

SCQ: social communication questionnaire; RBS-R: repetitive Behaviours Scale – Revised; SWAN-I: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour inattention subscale; SWAN-HI: Strengths and Weaknesses of ADHD-symptoms and Normal Behaviour hyperactivity/impulsivity subscale; FSIQ: full-scale intelligence quotient; CBCL-I: Child Behaviour Checklist internalizing problems subscale; CBCL-E: Child Behaviour Checklist externalizing problems subscale



Supplemental Figure 1: Effect sizes (eta-squared) for significant between-dataset differences in deviations from age-related models for the females (left) and males (right) from the matched sample when the models were built using each dataset (HBN: Healthy Brain Network, POND: Province of Ontario Neurodevelopmental network).



Supplemental Figure 2: Significant association between (A) the deviations from age models of cortical surface area and intelligence (FSIQ) and (B) the deviations from connectivity strength models and head motion. FSIQ: full-scale intelligence quotient

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