Neurostats Reading Group

Neuroanatomical diversity of corpus callosum and brain volume in autism: meta-analysis, analysis of the Autism Brain Imaging Data Exchange (Abide) project, and simulation

A. Lefebvre, A. Beggiato, T. Bourgeron, R. Toro (2015)

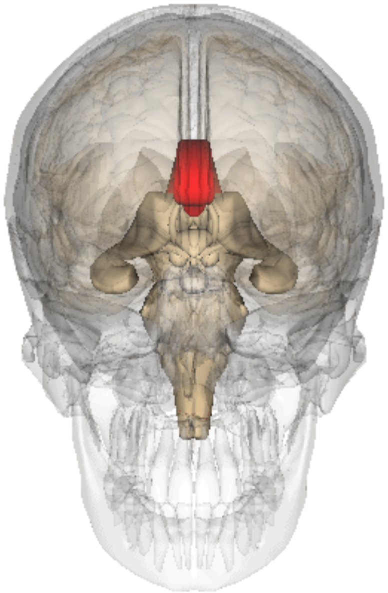
Camille Maumet, February 26th 2015

THE UNIVERSITY OF WARWICK

Motivation

- Many reports outlining **smaller corpus callosum (CC) in Autism** Spectrum Disorders

- Comparison between
  - Meta-analysis
  - Analysis of ABIDE cohort
- Simulations



META-ANALYSIS

Data collection

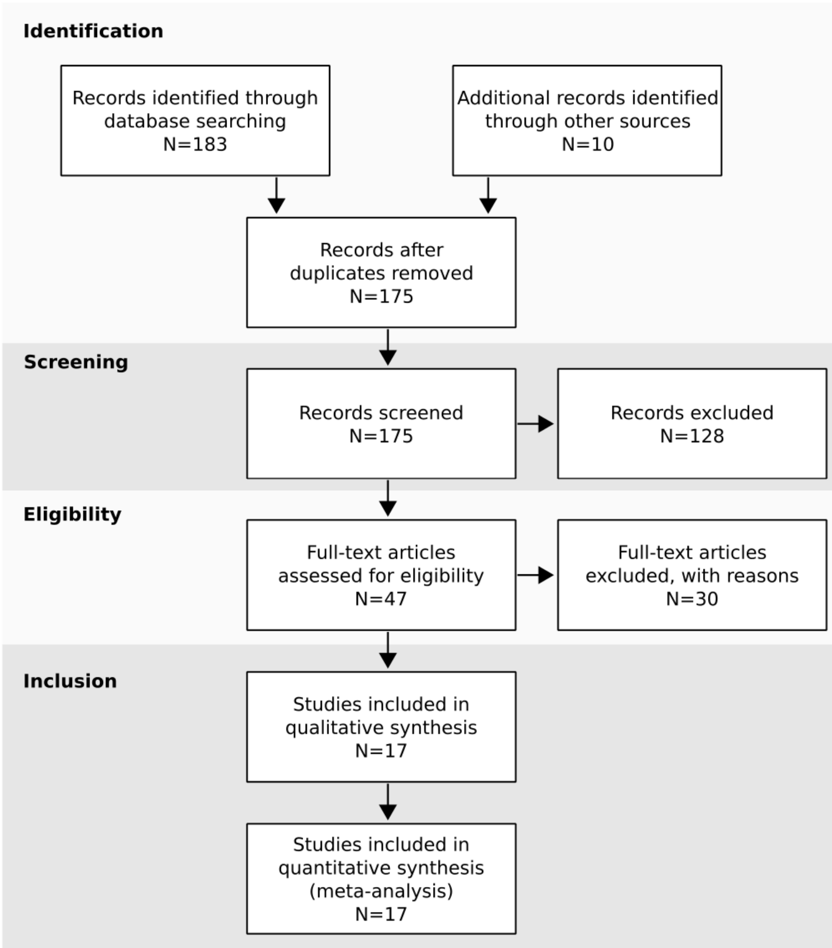


Figure S1. Flow diagram for the inclusion of articles in the meta-analysis.

<u>All studies from:</u> Frazier and Hardan (2009)

<u>Pubmed search</u>: (autism OR PDD OR "pervasive developmental disorder") AND "corpus callosum"

<u>Exclusion:</u> "excluded those that did not report measurements of corpus callosum size and standard deviation for patients and controls"

980 subjects, 521 patients and 459 controls

Data collection

Table 3. Meta-analysis: Mean CC size, effect size, significance of the difference, statistical power. The different values were scaled to provided measurements in cm^2 (This scaling does not affect our meta-analysis, which was performed on standardised mean differences).

Reference	N_{ASD}	N_{Ctrl}	Mean CC_{ASD} ±SD (cm^2)	Mean CC_{Ctrl} ±SD (cm^2)	Effect Size	P-Value (2-sided)	Power to detect SD=0.3 (2-sided)
Gaffney 1987 (36)	13	35	5.89±1.04	6.24±1.37	-0.27	0.41	17.3%
Egaas 1995 (37)	51	51	5.57±0.99	5.89±0.91	-0.33	0.097	32.3%
Piven 1997 (38)	35	36	6.15±0.83	6.40±0.38	-0.39	**0.11**	24.1%
Manes 1999 (39)	27	17	4.64±0.99	5.71±0.97	-1.07	**0.0011**	16.2%
Elia 2000 (40)	22	11	5.26±1.00	5.41±0.64	-0.16	0.67	12.7%
Rice 2005 (41)	12	8	7.34±1.11	7.75±1.14	-0.35	0.45	9.3%
Vidal 2006 (42)	24	26	6.06±1.15	6.68±0.79	-0.62	**0.033**	17.9%
Boger 2006 (43)	45	26	4.59±0.67	4.99±0.72	-0.57	**0.022**	24.1%
Alexander 2007 (44)	43	34	7.87±1.99	9.32±1.70	-0.77	**0.012**	25.2%
Just 2007 (3)	18	18	6.40±0.88	7.1±0.88	-0.78	**0.025**	13.9%
Hardan 2009 (45)	22	23	5.74±1.13	6.58±1.04	-0.76	**0.014**	16.2%
Freitag 2009 (46)	15	15	6.22±0.45	6.54±1.24	-0.34	0.36	12.2%
Keary 2009 (47)	32	34	6.19±1.09	6.76±1.10	-0.51	**0.040**	22.4%
Anderson 2011 (48)	53	39	6.54±1.20	7.05±0.90	-0.46	**0.031**	29.6%
Hong 2011 (49)	18	16	8.14±1.31	8.27±1.27	-0.10	0.78	13.3%
Frazier 2012 (50)	23	2	6.30±1.11	6.78±1.08	-0.43	0.15	16.7%
Prigge 2013 (51)	68	47	5.74±0.91	6.24±0.89	-0.55	**0.0044**	36.0%

Effect size, power and sample size

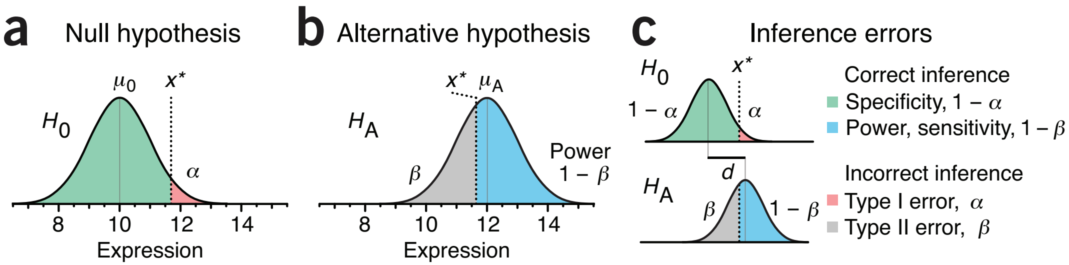
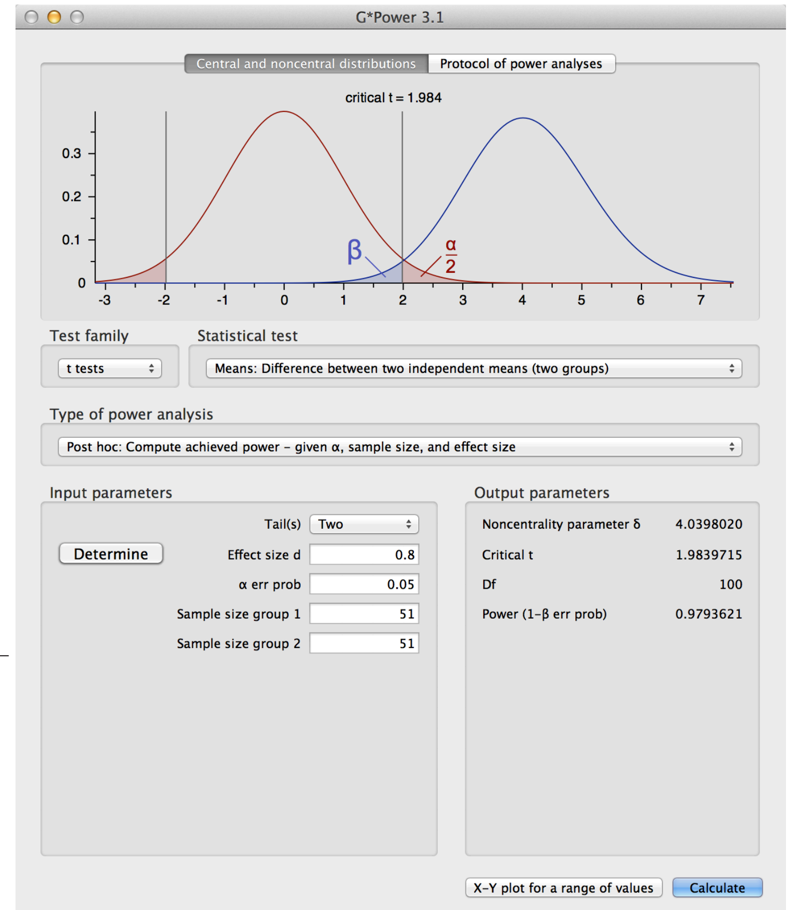


Figure 2 | Inference errors and statistical power. (**a**) Observations are assumed to be from the null distribution (H_0) with mean μ_0. We reject H_0 for values larger than x^* with an error rate α (red area). (**b**) The alternative hypothesis (H_A) is the competing scenario with a different mean μ_A. Values sampled from H_A smaller than x^* do not trigger rejection of H_0 and occur at a rate β. Power (sensitivity) is $1 - \beta$ (blue area). (**c**) Relationship of inference errors to x^*. The color key is same as in **Figure 1**.

<u>Source:</u> Krzywinski, M., & Altman, N. (2013). Points of significance: Power and sample size. Nature Methods, 10(12), 1139–1140. doi:10.1038/nmeth.2738



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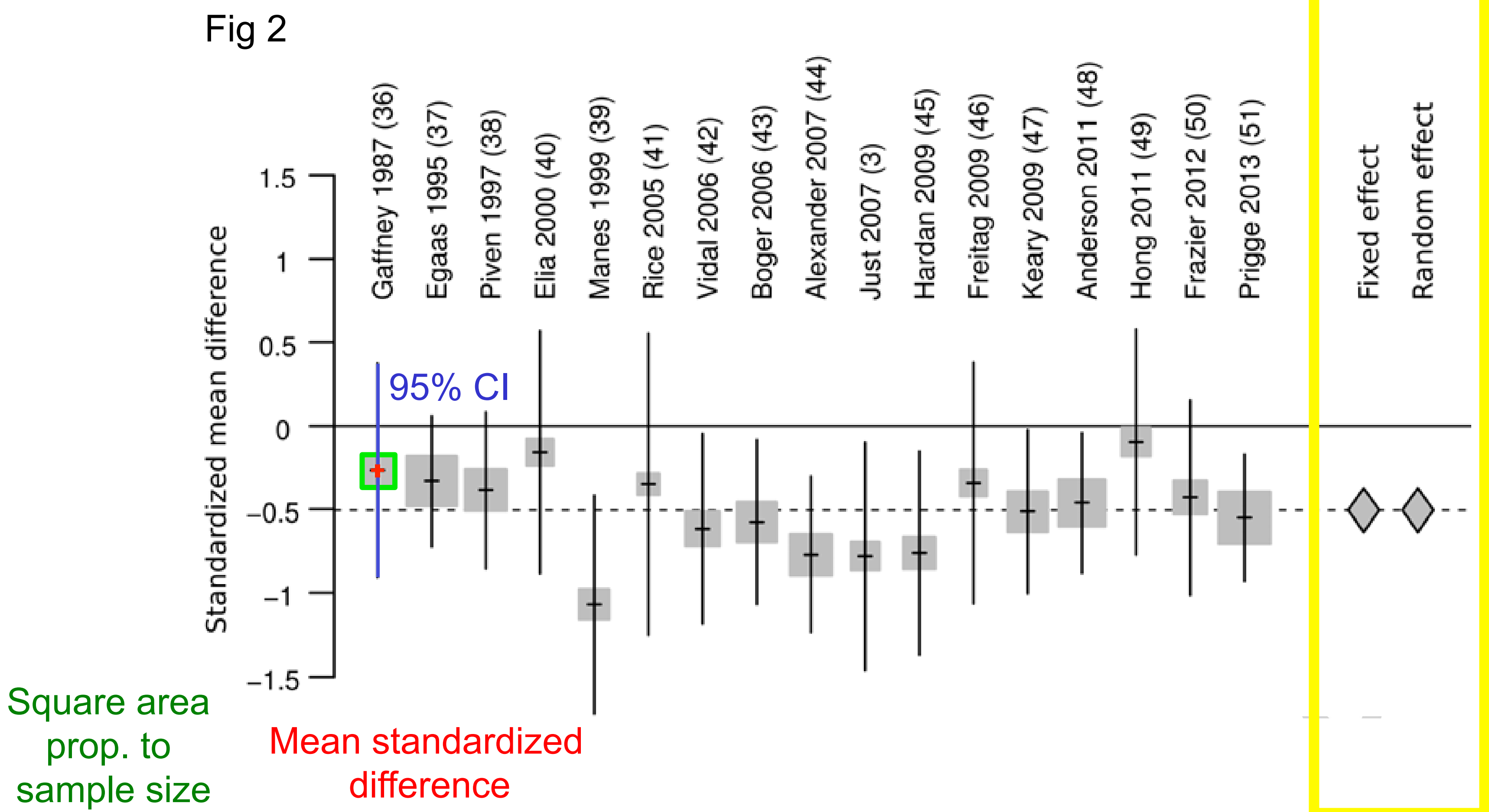
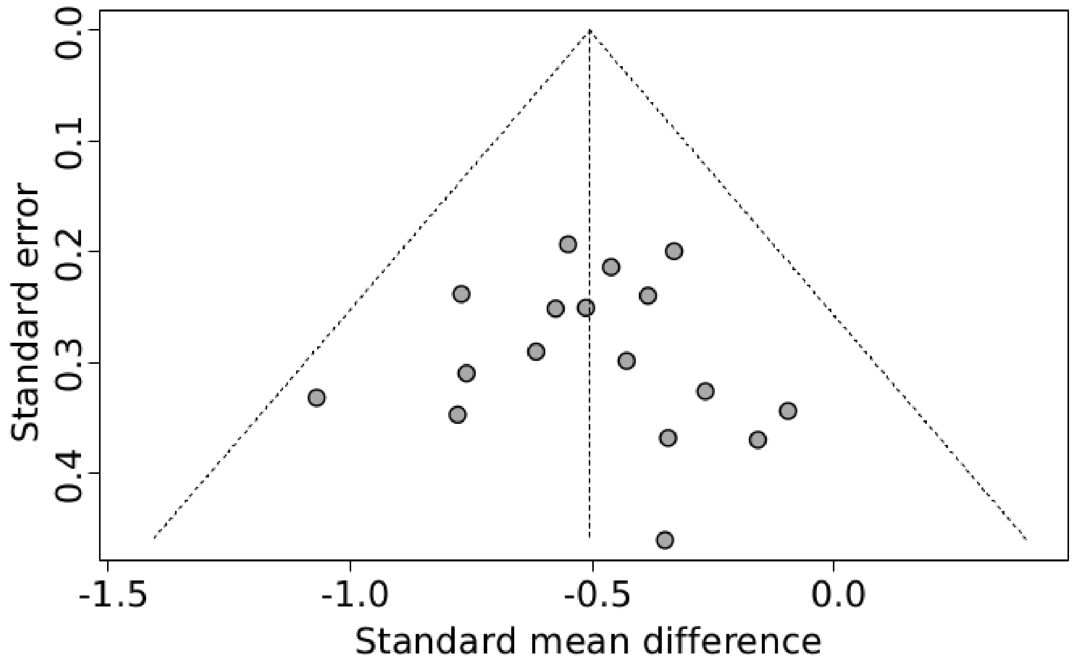
Results: Forest plot



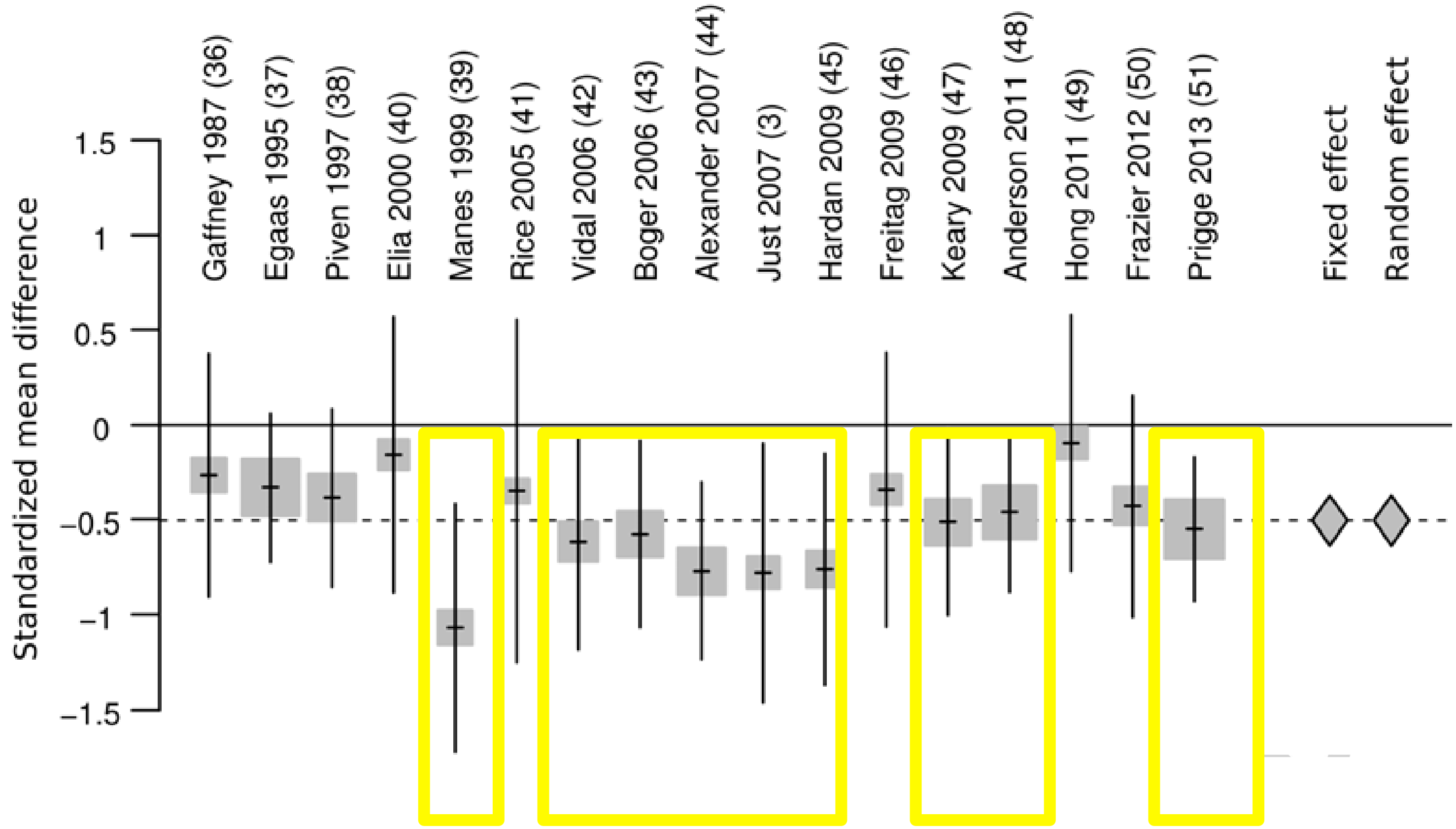
Publication Bias: Funnel plot

Fig 3



Selective publication bias

Fig 2



ABIDE

Autism Brain Imaging Data Exchange

ANALYSIS OF ABIDE

Abide Dataset

- 1102 subjects with T1w
- Freesurfer segmentations
- Exclusions
  - QC: 380 subjects excluded
  - Age: 28 subjects excluded

ABIDE
Autism Brain Imaging
Data Exchange

694 subjects, 328 patients and 366 controls

(IQ for 672 subjects)

Behavioral characteristics

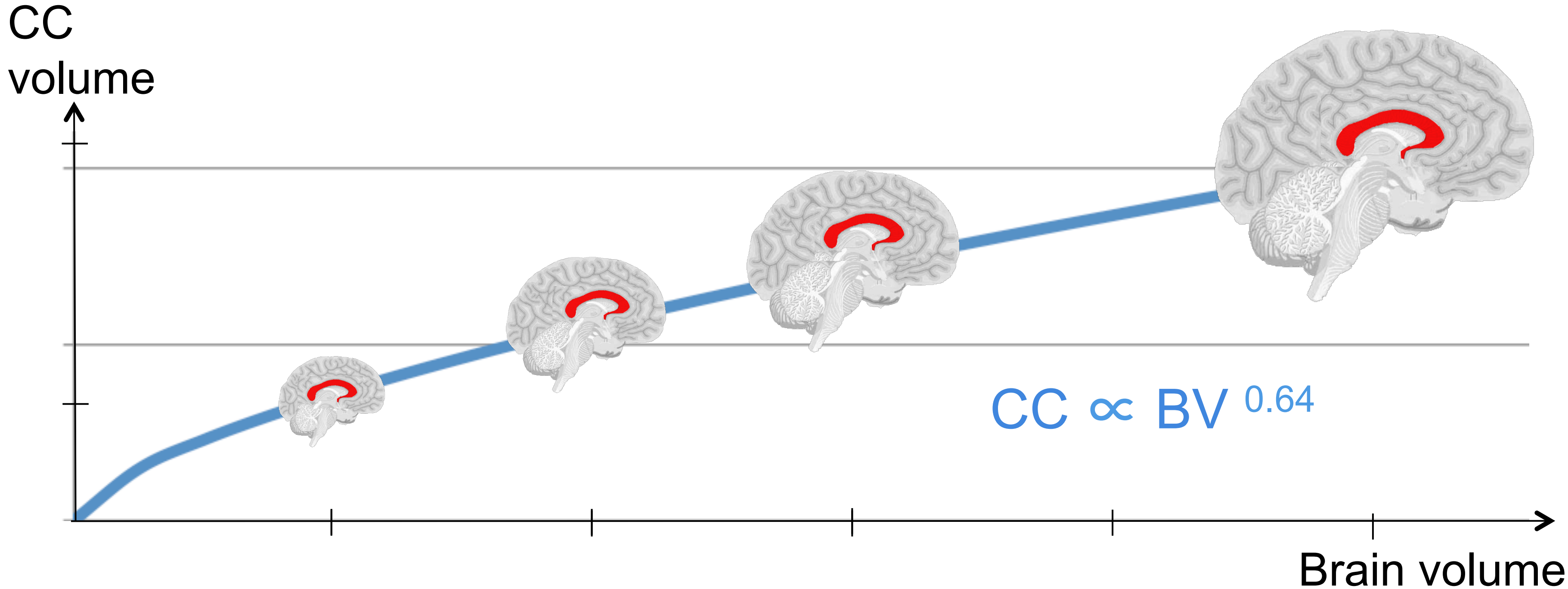
- Sample
  - 415 subjects with Autism Diagnostic Observation Schedule (ADOS) scores.
  - 672 subjects with IQ
- Significant Differences:
  - Social Responsiveness Scale ($p<0.0001$)
  - Autism Quotient scores ($p<0.0001$)
  - Full IQ (-6 points, $p<0.00001$)
    - mainly due to Verbal IQ (-8 points, $p<0.00001$)
    - No signif. difference in Performance IQ.

Effect of age, sex, scanning site, and diagnostic group

Table 4. Site, Age, Sex and Group effects in ICV, BV and CC.	Intra-Cranial Volume **ICV**	Brain Volume **BV**	Volume of Corpus Callosum **CC**
Mean Size (cm^3)±SD	1368±231	1131±130	3.16±0.54
Site Effect			
F	32.8	10.6	10.7
P-Value	<0.0001	<0.0001	<0.0001
R^2	43.7%	20.1%	20.2%
Age Effect			
Increase (cm^3/year)	4.3	2.3	0.019
F	12.19	10.86	45
P-Value	0.0005	0.001	<0.0001
R^2	1.7%	1.5%	6.1%
Sex Effect			
Percent Difference (1-Female/Male)	9.4%	9.3%	7.4%
F	28.2	62.11	17.1
P-Value	<0.0001	<0.0001	<0.0001
R^2	3.9%	8.2%	2.4%
Group Effect			
Difference (cm^3)	6.8	4	-0.007
F	0.26	0.03	0.35
P-value	0.61	0.86	0.56
R^2	0.00	0.00	0.00
Variance explained by the full model	46.9%	26.0%	22.0%

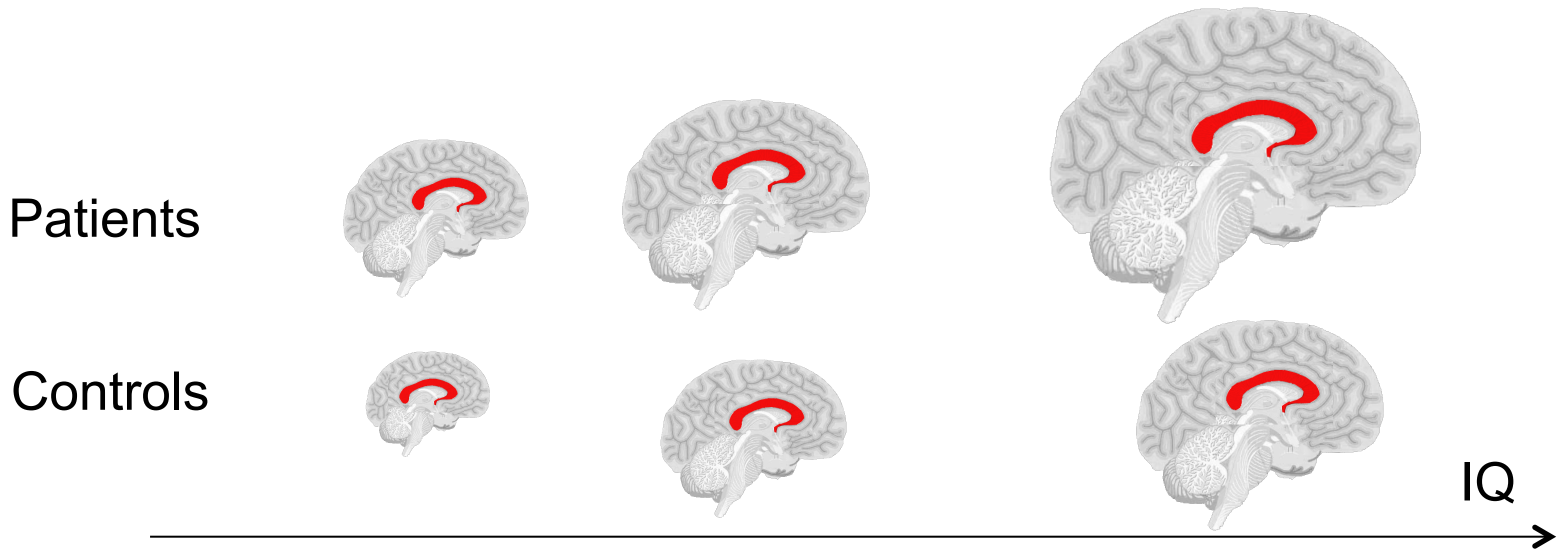
Effect of brain volume on CC volume

- CC depends on BV non-linearly
  - Larger brain have prop. smaller CC
  - No signif. difference between-group



Effect of brain volume on IQ

- IQ ~ site + age + sex + BV + group + BV*group
  - **Group** effect ($p<0.0001$): IQ smaller in patients (same BV)
  - **Interaction Group*BV** ($p=0.0178$): increases in BV resulted in smaller increase in IQ in patients.



SIMULATIONS

Normalization w.r.t BV / IQ

- BV: 2 main approaches
  - Use proportion of BV as units
  - Add BV and group*BV as covariate of no interest in design matrix

- IQ matching across groups

BV normalization

Power to detect artefactual Group effect on CC

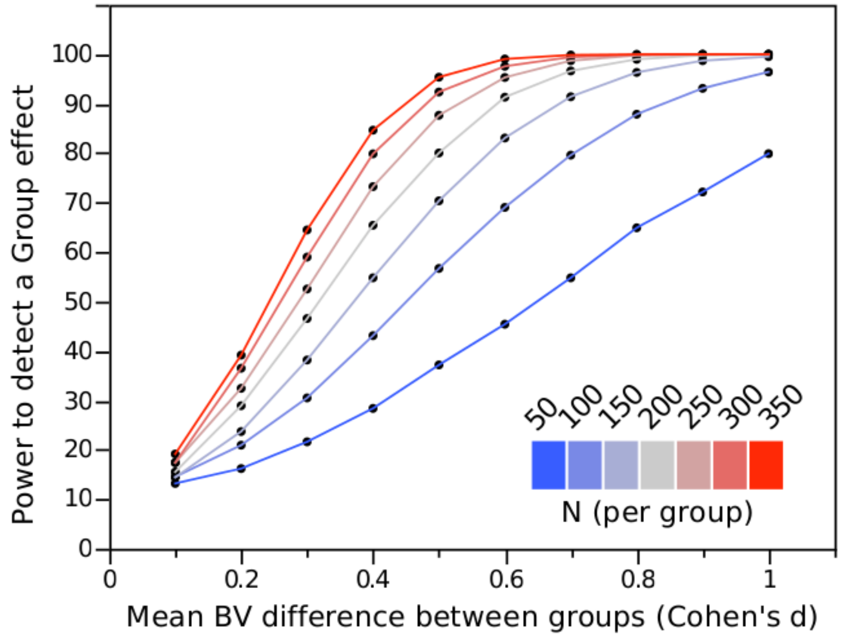


Figure S5. Statistical power to detect a significant, artefactual difference in CC size for two groups presenting a difference in mean BV: CC normalized by BV. Statistical power as a function of the difference in mean BV between 2 simulated groups (Cohen's d) consisting of 50, 100, … 350 subjects each. CC is normalized by dividing it by BV. Because of the non-linear relationship between CC and BV, CC normalization was not sufficient to control for the difference in mean BV.

BV covariation

Power to detect artefactual Group effect on CC

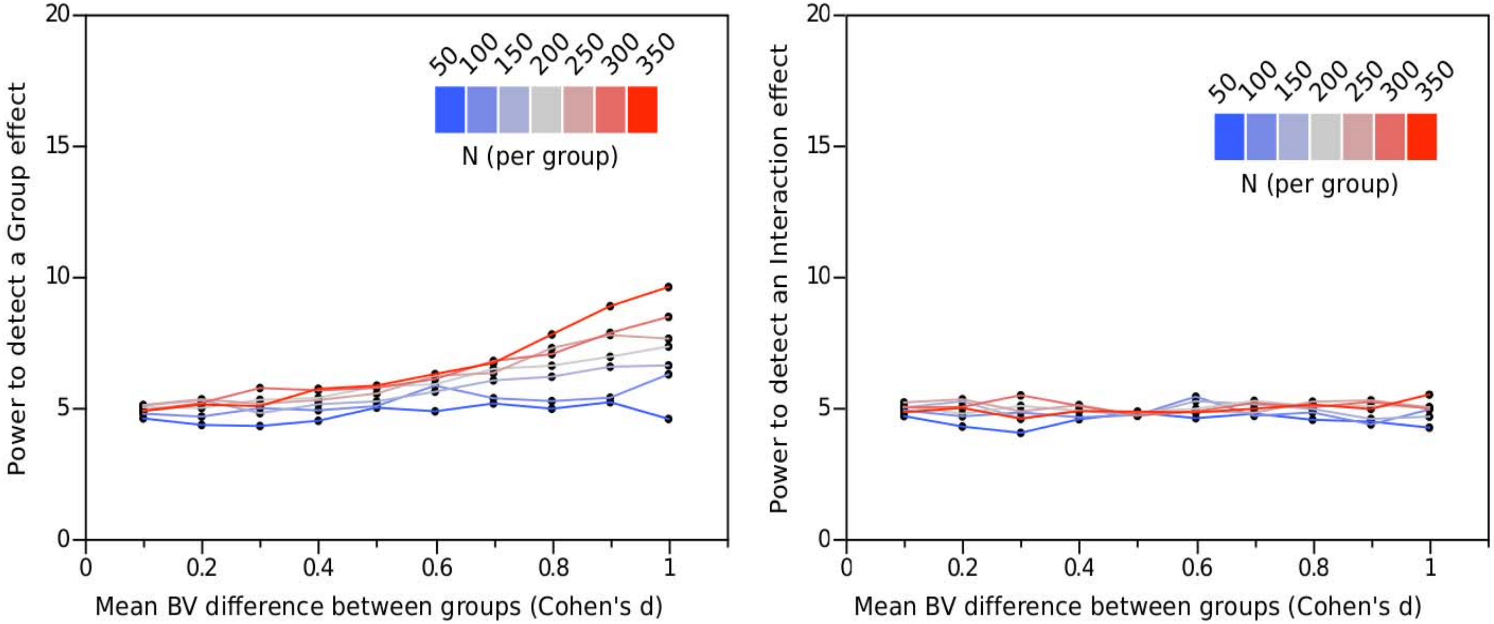


Figure S6. Statistical power to detect a significant, artefactual difference in CC size between two groups presenting a difference in mean BV: BV used as covariate in a GLM. (a) Statistical power to detect a group effect in CC size as a function of the difference in mean BV between 2 simulated groups (Cohen's d) consisting of 50, 100, …, 350 subjects each. (b) Statistical power to detect an interaction effect BV*Group in CC size as a function of the difference in mean BV between 2 simulated groups consisting of 50, 100, …, 350 subjects each. Including BV as a covariate successfully controls for BV effects even for large sample sizes and large differences in mean BV.

IQ matching

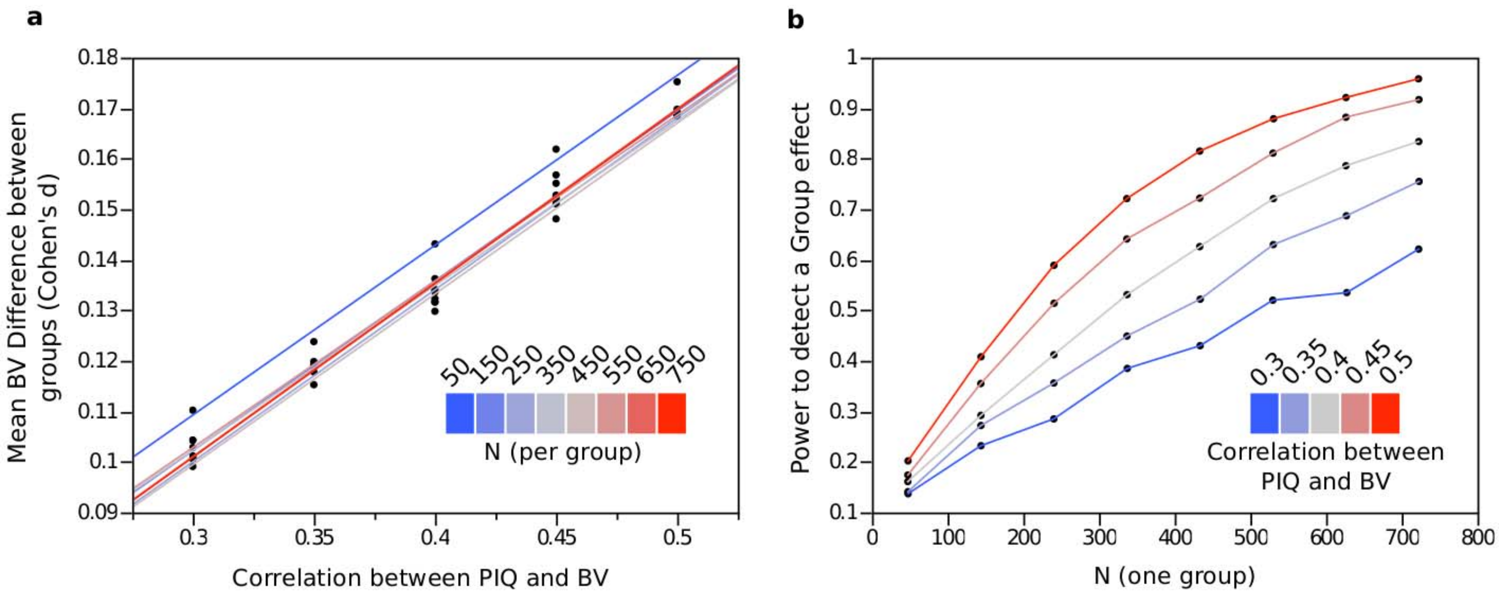


Figure S7. Effect of IQ matching on mean BV. Two groups were simulated with different correlation between FIQ and BV. In one (the control group) both VIQ and PIQ correlated with BV. In the other (the ASD group) only PIQ correlated with BV. FIQ was computed as the average between VIQ and PIQ, and subjects in both groups were selected to match the FIQ distributions. (a) Mean BV difference induced by matching two populations as a function of the correlation between PIQ and BV, for groups of 50, 150, …, 750 subjects each. (b) Power to detect a difference in mean BV induced by matching two populations by FIQ as a function of the number of subjects per group. Statistical power curves were drawn for correlations between PIQ and BV of 0.3, 0.35, …, 0.5.

DISCUSSION

CC size in Autism

- Significant effect detected by meta-analysis
- No significant effect when taking into account site, age and sex.
- Non-linear variations of CC with BV might explain the difference.

………………… => Data Sharing