The need for nonhuman primate models of neurodevelopmental disorders - Autism

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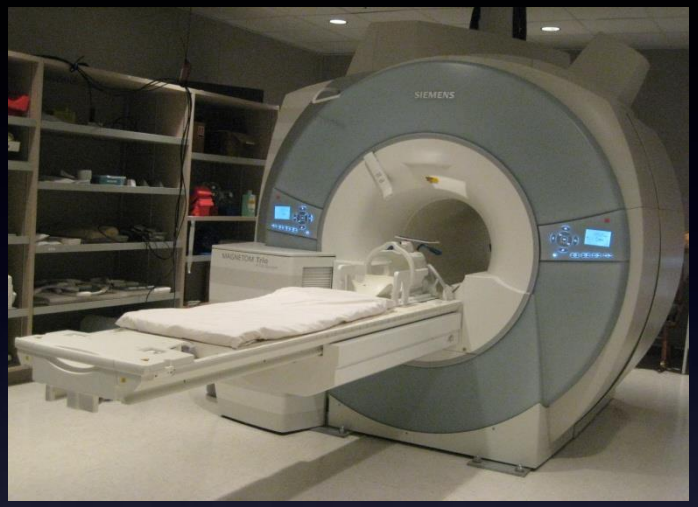
Brain Development in ASD

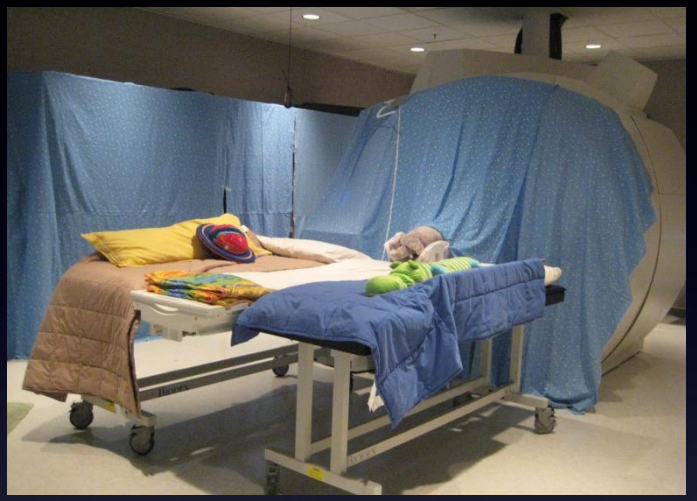
Magnetic resonance imaging
provides evidence of different types of ASD

Child-friendly scanning environment

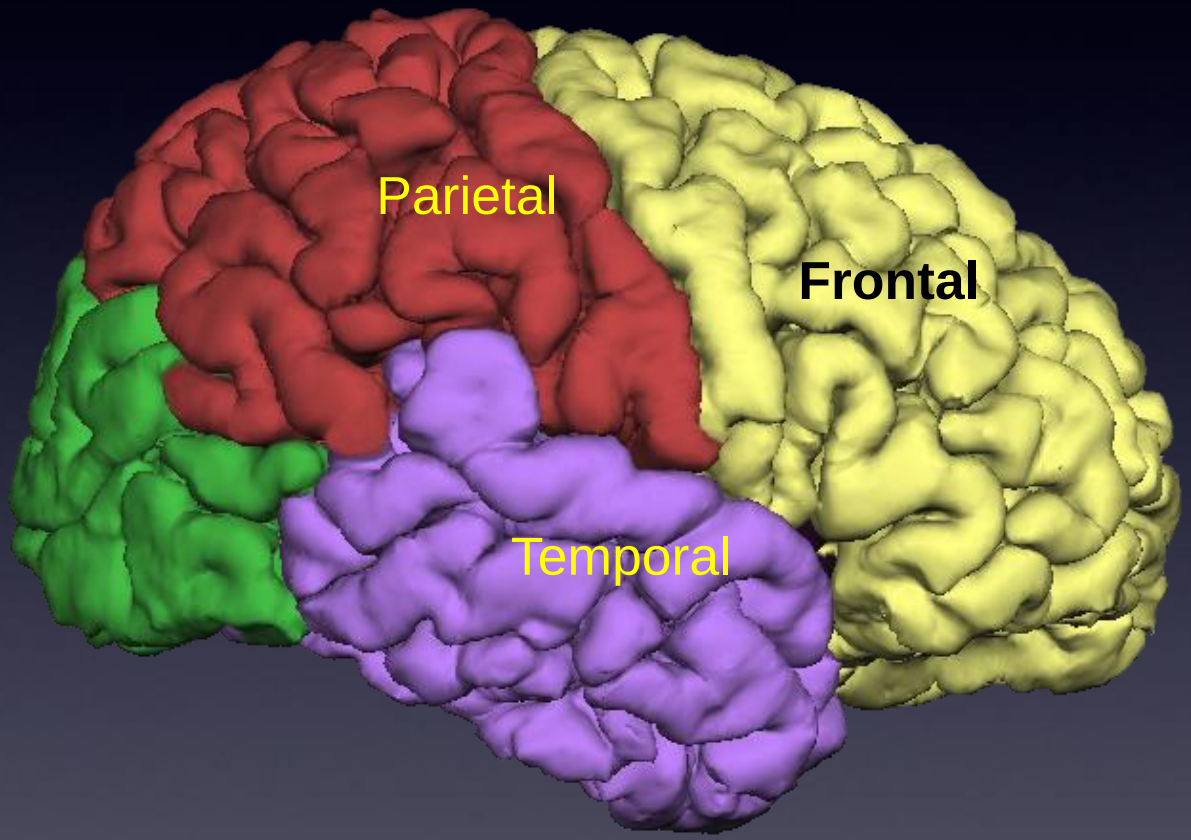
Before



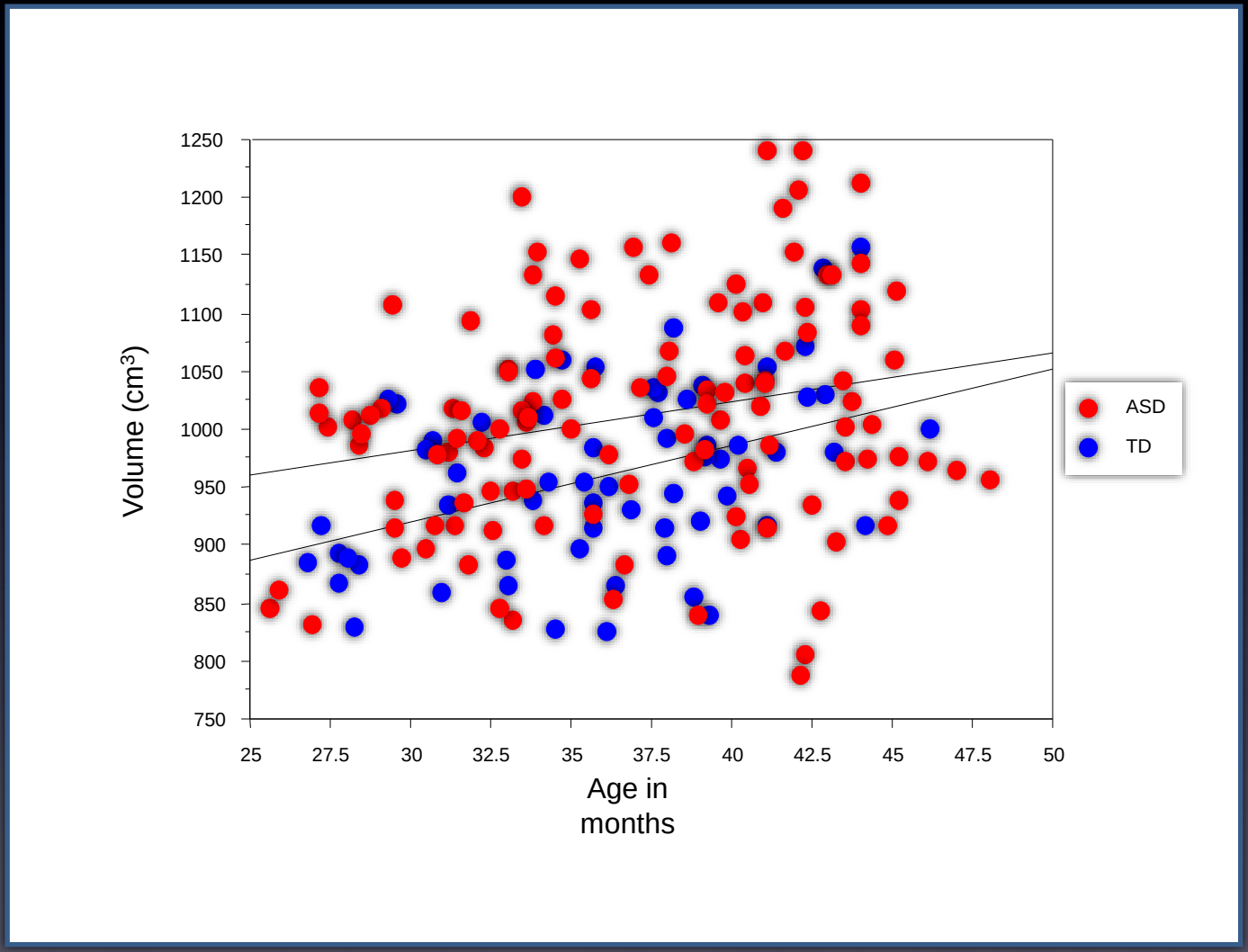
After



Total Brain Measurements



Total brain size is on average larger but extremely variable in ASD



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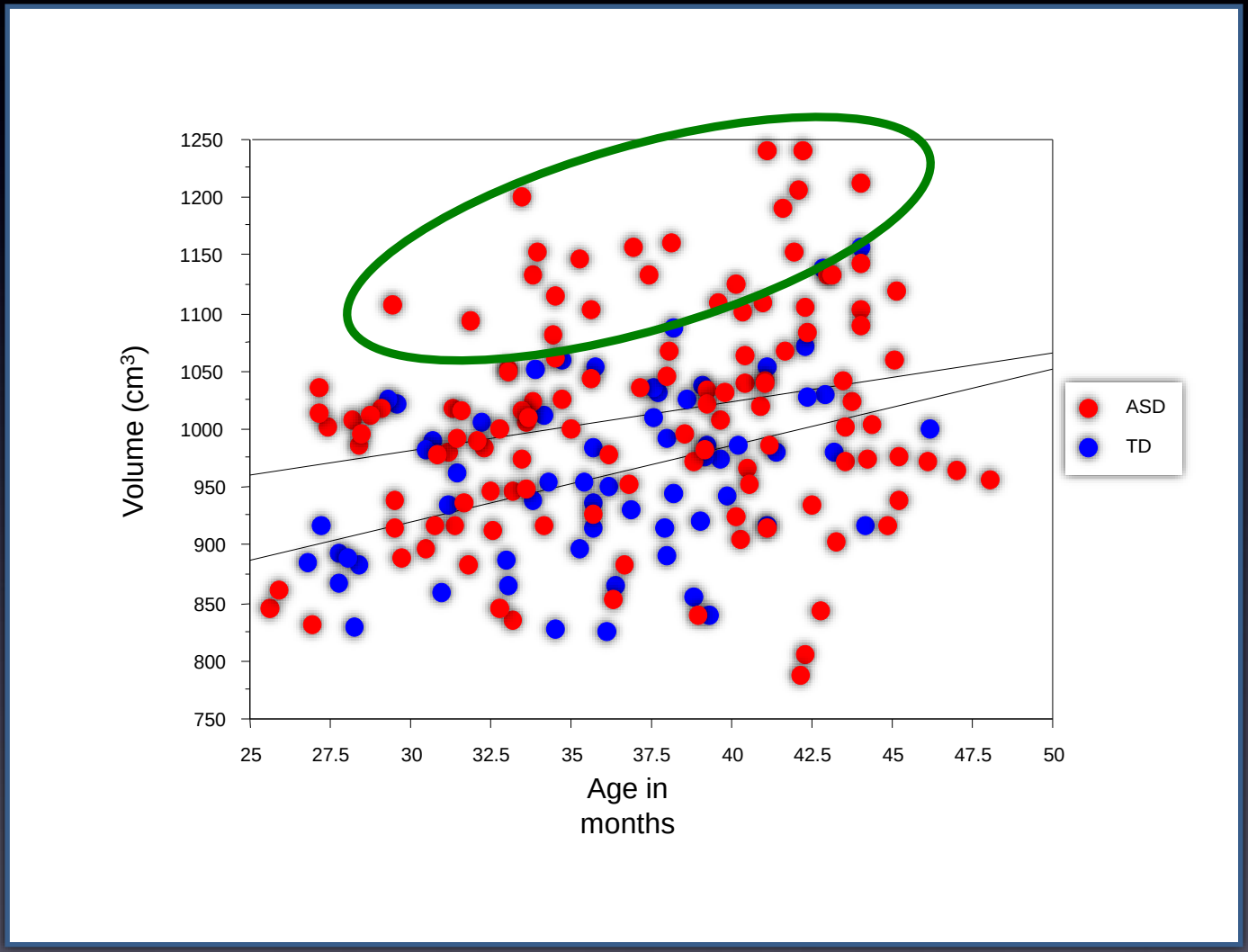
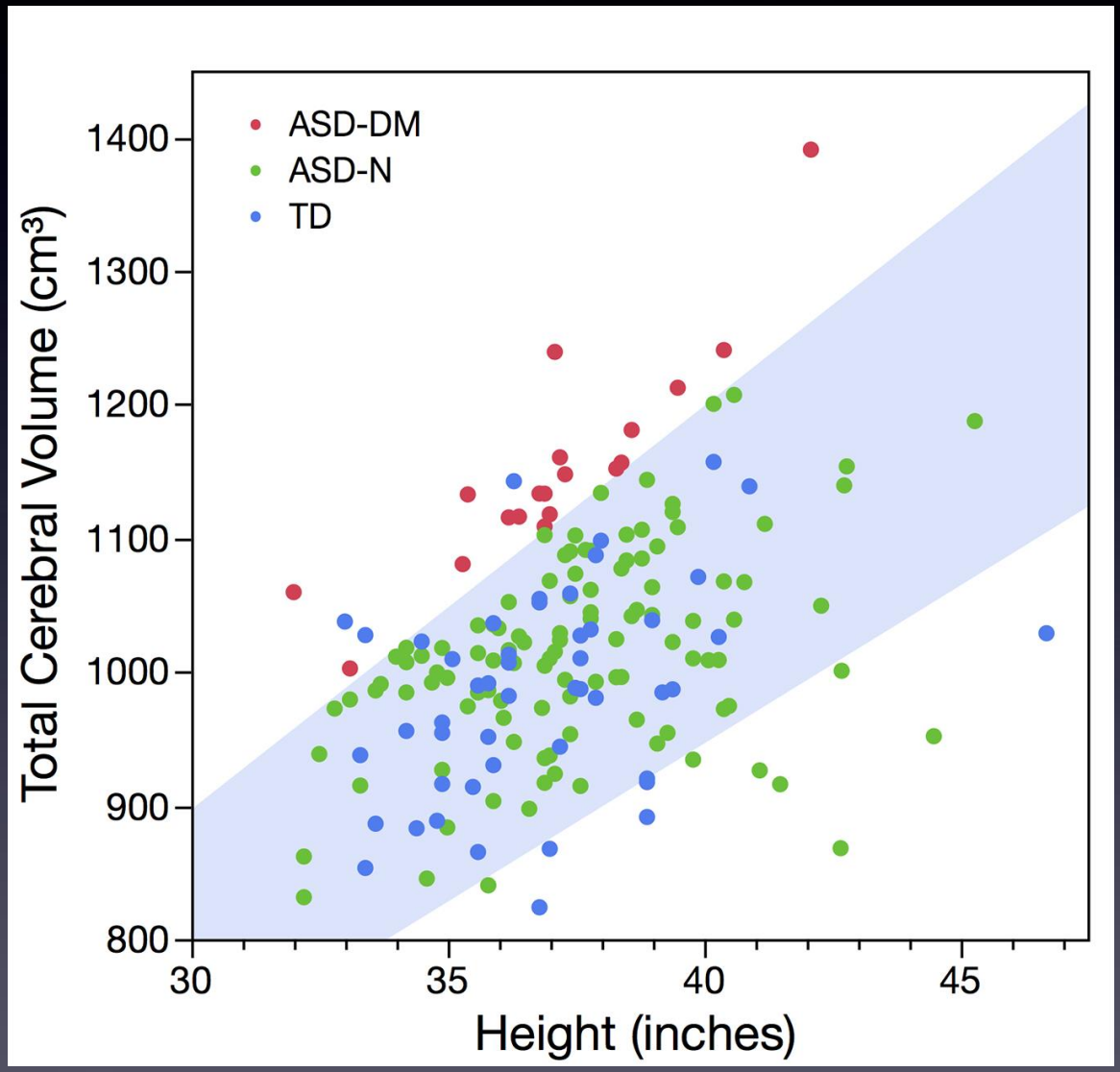


Distribution of Brain Size/Height for Boys in APP



Disproportionate Megalencephaly (ASD-DM)

Disproportionate Megalencephaly (ASD-DM)
i.e. the ratio of brain volume to height is 1.5 standard deviations above control mean

Disproportionate Megalencephaly (ASD-DM)

Boys

85% 15%

Typical Child
Age 31 months
TCV 981.96

Autism
Normal brain size
Age 32 months
TCV 984.57

Autism
Megalencephaly
Age 30 months
TCV 1180.98

More surface area of the cortex
But not thicker cortex

Typical Child
Age 31 months
TCV 981.96

Autism
Normal brain size
Age 32 months
TCV 984.57

Autism
Megalencephaly
Age 30 months
TCV 1180.98

Are there behavioral, cognitive or biomedical differences between ASD-N and ASD-DM?

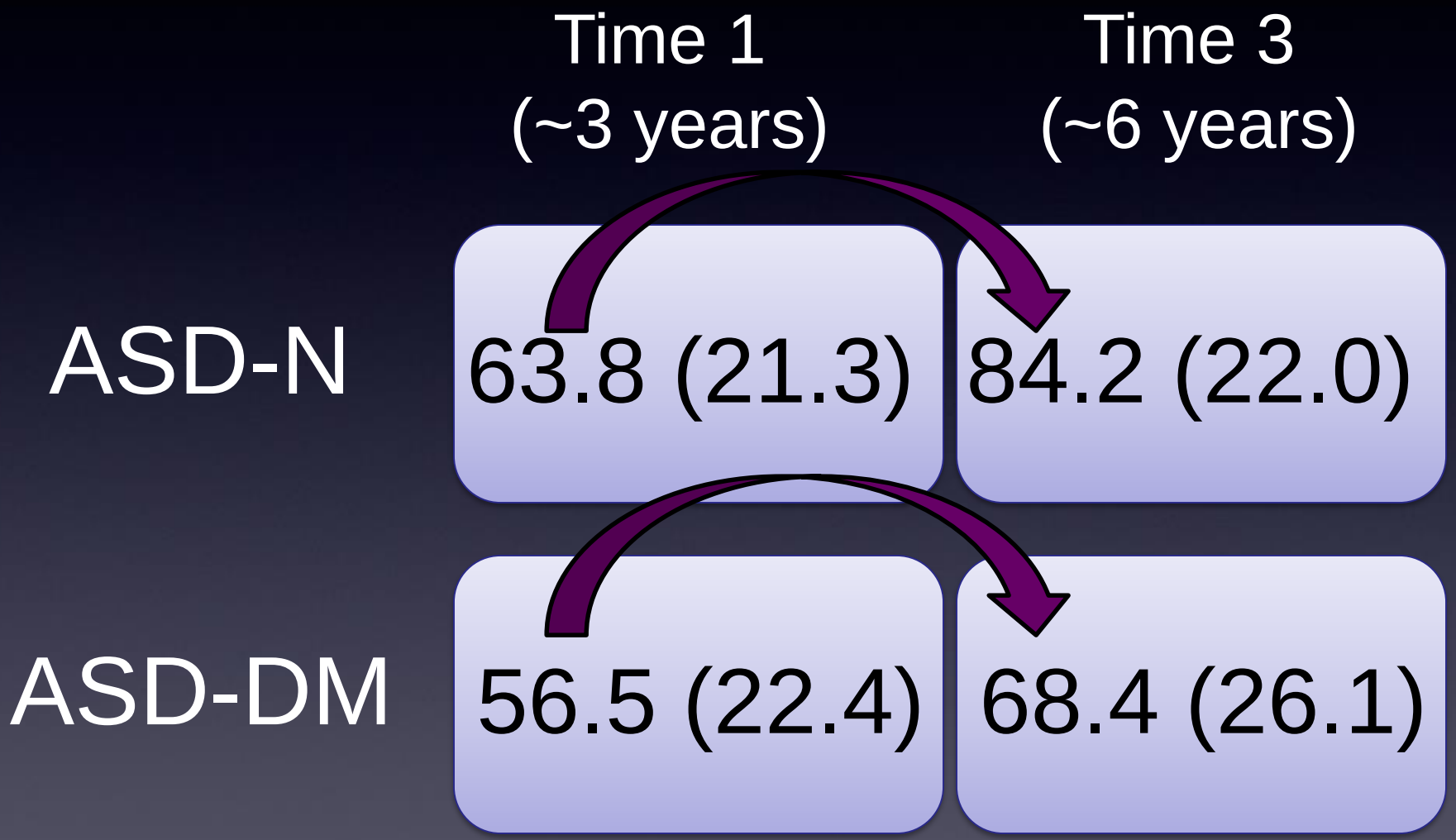
COMMENTARY

In Pursuit of Neurophenotypes: The Consequences of Having Autism and a Big Brain

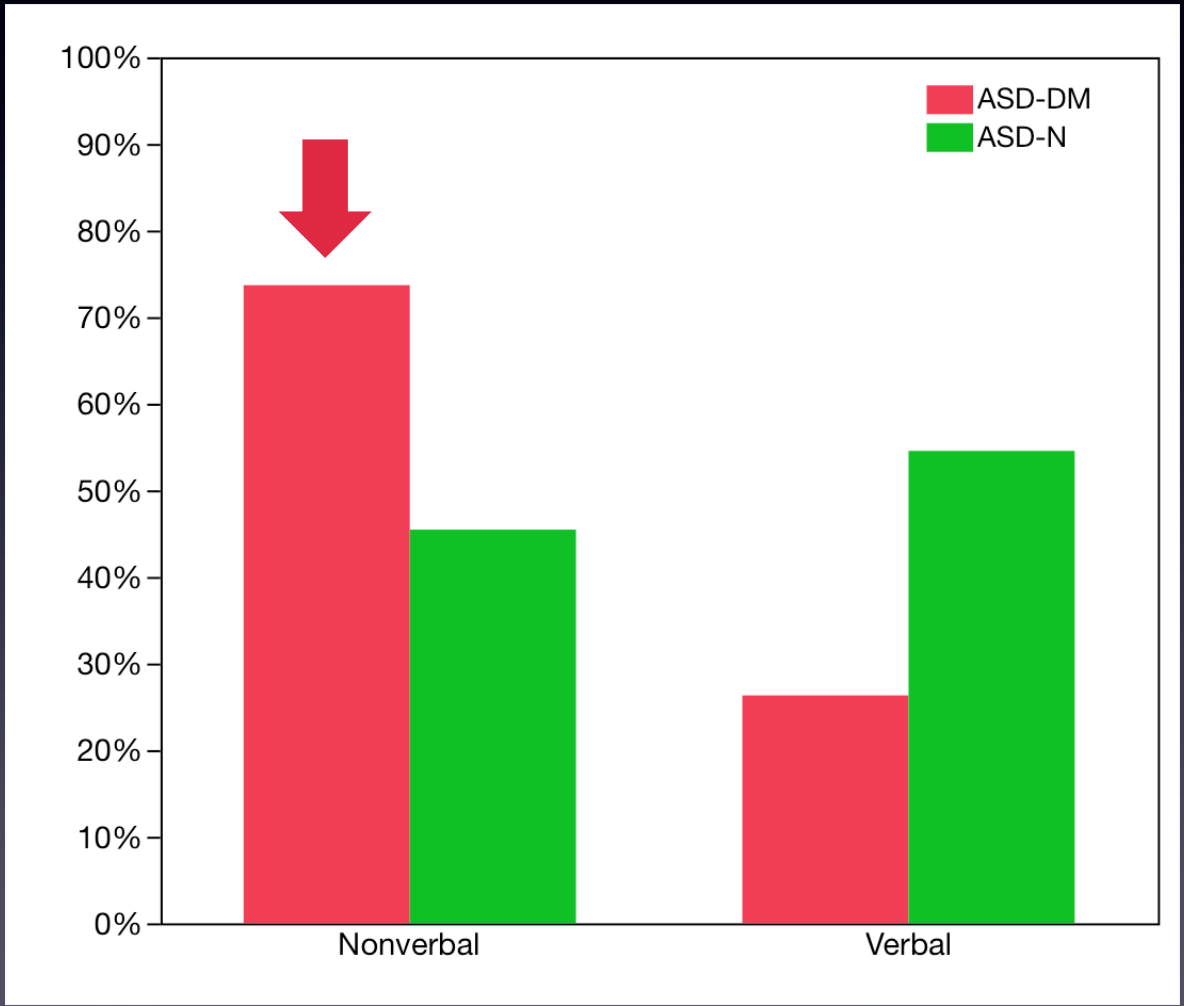
David G. Amaral, Deana Li, Lauren Libero, Marjorie Solomon, Judy Van de Water, Ann Mastergeorge, Letitia Naigles, Sally Rogers, and Christine Wu Nordahl

Autism Res *2017, 10: 711–722.*

IQ
in ASD-N and ASD-DM boys



Relationship between language and brain size in ASD-DM and ASD-N Boys



CHD8 and Autism

Cell

Disruptive *CHD8* Mutations Define a Subtype of Autism Early in Development

Raphael Bernier,[1,19] Christelle Golzio,[2,19] Bo Xiong,[3,19] Holly A. Stessman,[3,19] Bradley P. Coe,[3,19] Osnat Penn,[3] Kali Witherspoon,[3] Jennifer Gerdts,[1] Carl Baker,[3] Anneke T. Vulto-van Silfhout,[4] Janneke H. Schuurs-Hoeijmakers,[4] Marco Fichera,[5,6] Paolo Bosco,[5] Serafino Buono,[5] Antonino Alberti,[5] Pinella Failla,[5] Hilde Peeters,[7,8] Jean Steyaert,[8,9,10] Lisenka E.L.M. Vissers,[4] Ludmila Francescatto,[2] Heather C. Mefford,[11] Jill A. Rosenfeld,[12] Trygve Bakken,[13] Brian J. O'Roak,[14] Matthew Pawlus,[15] Randall Moon,[15,18] Jay Shendure,[3] David G. Amaral,[16] Ed Lein,[13] Julia Rankin,[17] Corrado Romano,[5] Bert B.A. de Vries,[4] Nicholas Katsanis,[2] and Evan E. Eichler[3,18,*]

Cell *158*, 263–276, July 17, 2014

Table 2. Brief Description of Phenotypic Presentation of 15 Patients with *CHD8*-Truncating Single-Nucleotide Variants

Patient	12714.p1	13986.p1	Nij023486	APP_09580 – 100	11654.p1	13844.p1	14016.p1	Troina2659	12991.p1	12752.p1	Troina2037	Nij – 010878	14233.p1	14406.p1	Nij07 – 06646	Observed N (% of Sample)
Sex	M	M	F	M	F	M	M	M	M	F	F	M	M	M	M	
Age at testing (years)	4	5	15	6	12	8	8	13	16	4	41	11	16	13	17	
Macrocephaly	–	+	–	+	+	+	+	+	+	+	+	–	+	–	–	12 (80%)
Prominent supraorbital ridge	u	u	–	–	u	+	–	–	–	u	+	–	u	u	–	7/9 (78%)
Hypertelorism	u	u	+	+	+	u	+	–	+	u	+	–	u	u	–	6/9 (67%)
Down-slanted palpebral fissures	u	u	+	–	+	u	+	+	–	u	+	–	u	u	+	6/9 (67%)
Flat feet	u	u	–	–	u	–	–	+	–	u	–	–	u	u	+	2/9 (22%)
Tall	+	+	+	+	+	+	+	+	–	u	–	+	+	+	+	12/14 (86%)
Overweight	–	–		–	–	–	–	–	–	u	+	+	–	+	–	3/14 (21%)
ASD	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	13 (87%)
Intellectual disability	–	+	+	+	+	+	–	+	+	–	+	–	+	–	–	9 (60%)
Attentional problems	–	–	+	+	+	–	–	–	+	+	+	+	+	+	–	9 (60%)
Anxiety problems	+	–	–	–	–	–	+	–	+	+	–	–	–	–	–	4 (27%)
Seizures	–	–	–	–	+	–	+	–	+	–	–	–	–	–	–	3 (20%)
Regression	+	–	+	+	+	+	–	+	–	–	–	–	+	–	–	7 (47%)
GI problems	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	12 (80%)
Sleep problems	–	+	+	+	+	–	+	–	+	+	–	–	+	+	+	10 (67%)
C section	–	–	–	–	+	–	–	+	+	+	–	–	–	–	+	5 (33%)
Birth induction/ augmentation	+	+	–	–	+	–	+	–	+	–	–	–	–	+	–	6 (40%)

+, present; –, absent; u, unknown. Detailed phenotypic data are outlined for each patient in the above domains in Table S5. Where a denominator is indicated, unknown values were excluded from the percent of sample calculation.

Macrocephaly – 80%

Autism – 87%

Need for nonhuman primate model of autism

- We do not understand the neurobiology of megalencephaly in autism – and these children have a poorer prognosis
- The behavioral impairments and megalencephaly of autism primarily involve the prefrontal cortex which is primitive in rodents.
- Manipulations of CHD8 in rodents produces megalencephaly but not the behavioral characteristics typical of autism.

Need for nonhuman primate model of autism

- Nonhuman primates have brain organization and social behavior much more like that of humans.
- Manipulations of genes in NHP that produce autism with megalencephaly in humans (eg. CHD8) would provide the substrate for understanding and for developing targeted treatments.
- It is in our national interest to develop the capacity to produce genetically modified