Bi/CNS/NB 150: Neuroscience

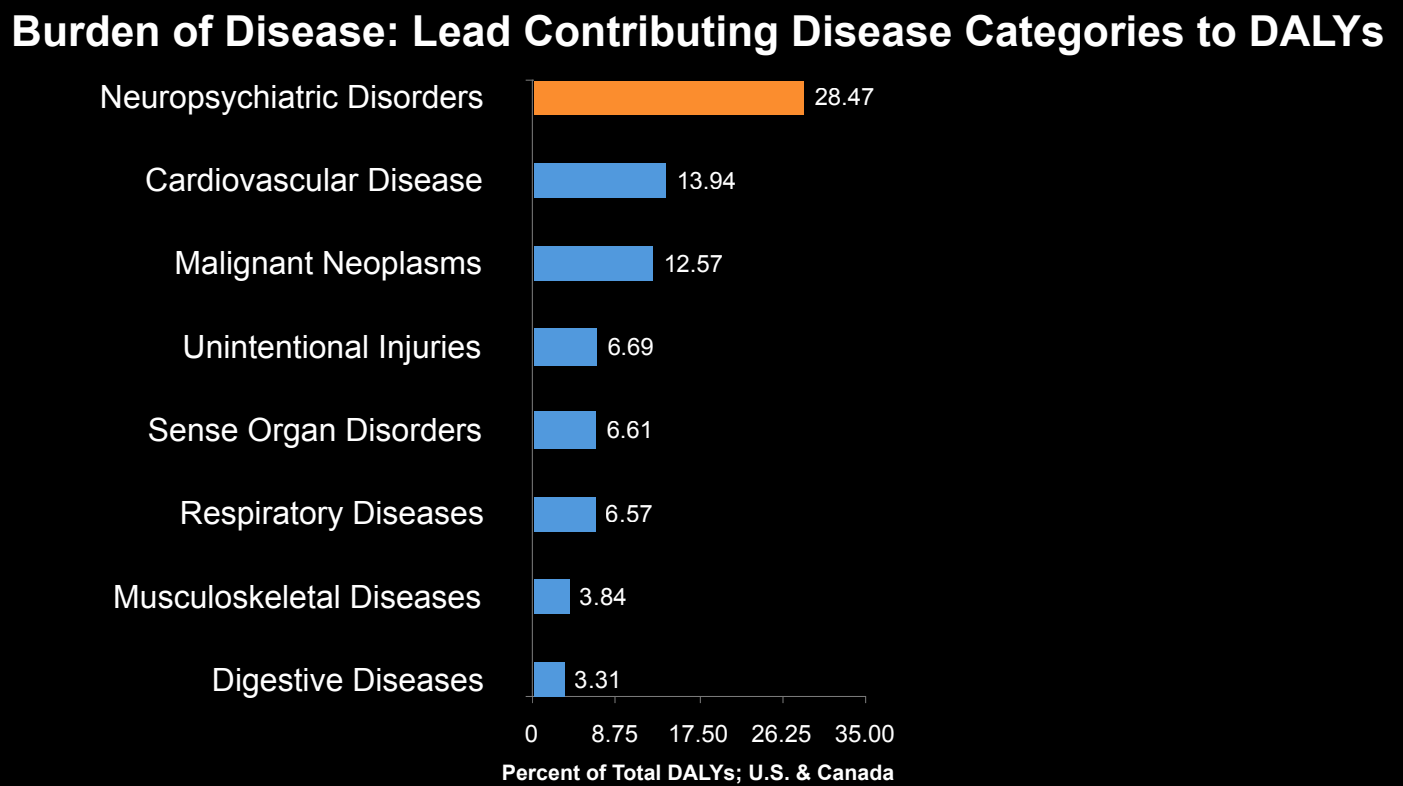
Lecture

Wednesday, Nov. 25, 2015
Ralph Adolphs

Autism

1

MORBIDITY FROM MEDICAL CAUSES



SOURCE: WHO 2008

What distinguishes brain diseases?

- The brain is extremely complex
(so it is hard to find the cause)

- The brain requires glucose and oxygen
(so cells can die easily)

- Most neurons do not divide after birth
(the brain cannot repair itself)

Two big challenges:

- Development
- Aging

3

What is Autism?

DSM Diagnosis
Research-quality Diagnosis
Research findings (genes, brain scans, etc.)

Autism Spectrum Disorders:
Pervasive Developmental Disorders

"there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits - and, I hope, will eventually receive - a detailed consideration of its fascinating peculiarities."

- Difficulties interacting with people
- Delayed and abnormal language
- Repetitive behaviors, desire for sameness

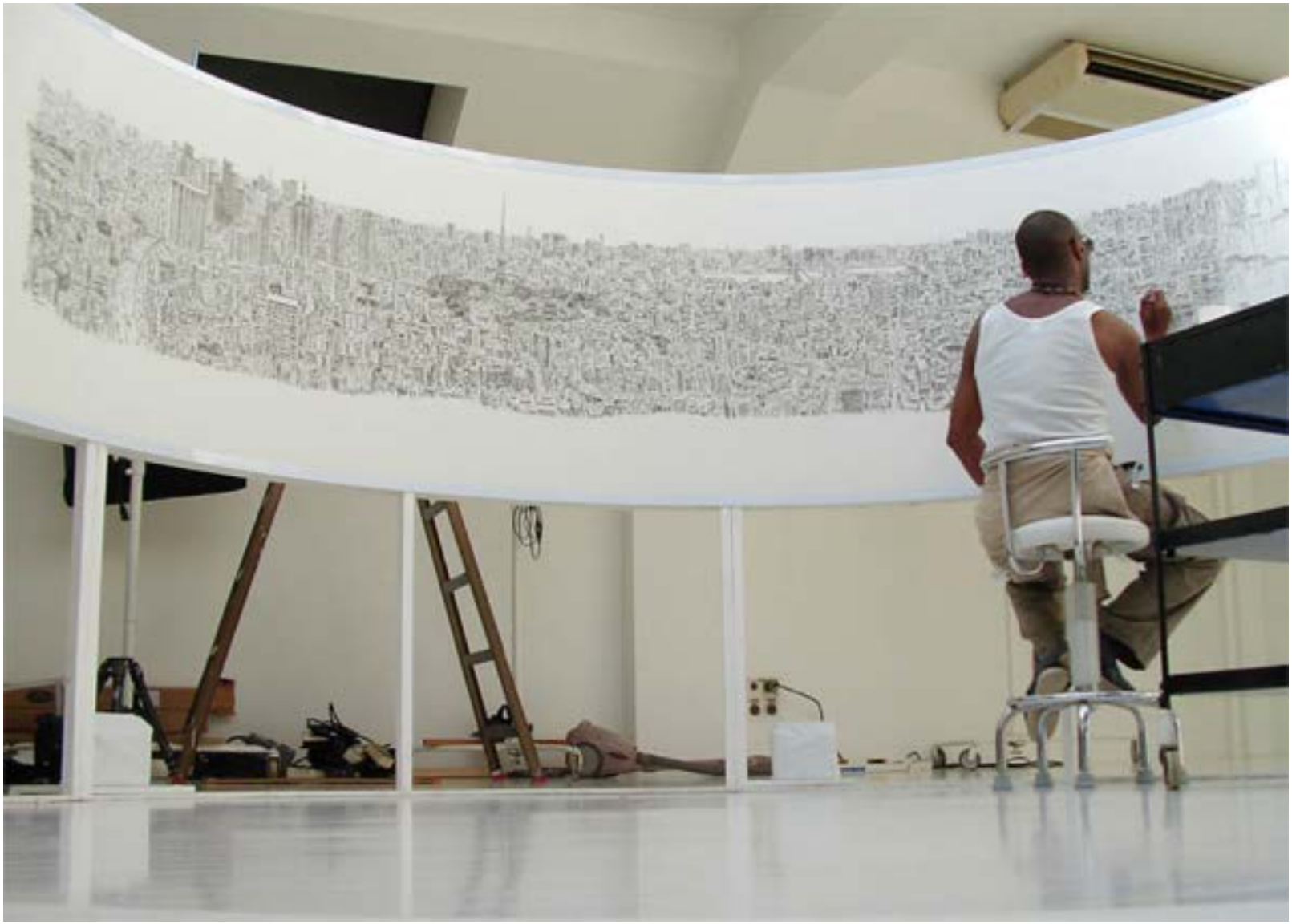
Kanner (1943). Autistic Disturbances of Affective Contact, *Nervous Child*, 2: 217-250.

Leo Kanner
"Autistic Disturbances of affective contact" 1943.

Hans Asperger (1944)
-lack of empathy,
"little professors"

Temple Grandin: NOT your typical person with autism

Stephen Wiltshire



DSM-IV Criteria (autism)

- **Social Impairments**
  - Lack of social or emotional reciprocity
  - Diminished gaze, facial expression, or body posture which would normally regulate social interaction
  - Marked difficulty sharing enjoyment with others
- **Communication Deficits**
  - Language delay
  - Echolalia—stereotyped language
  - Reciprocal conversation skills—language pragmatics
- **Stereotyped Interests and Rigid or Repetitive behavior**
  - Unusual interest (intensity or content)
  - Inflexible adherence to routines
  - Motor stereotypies
  - Preoccupation with parts of objects

How accurate is diagnosis?

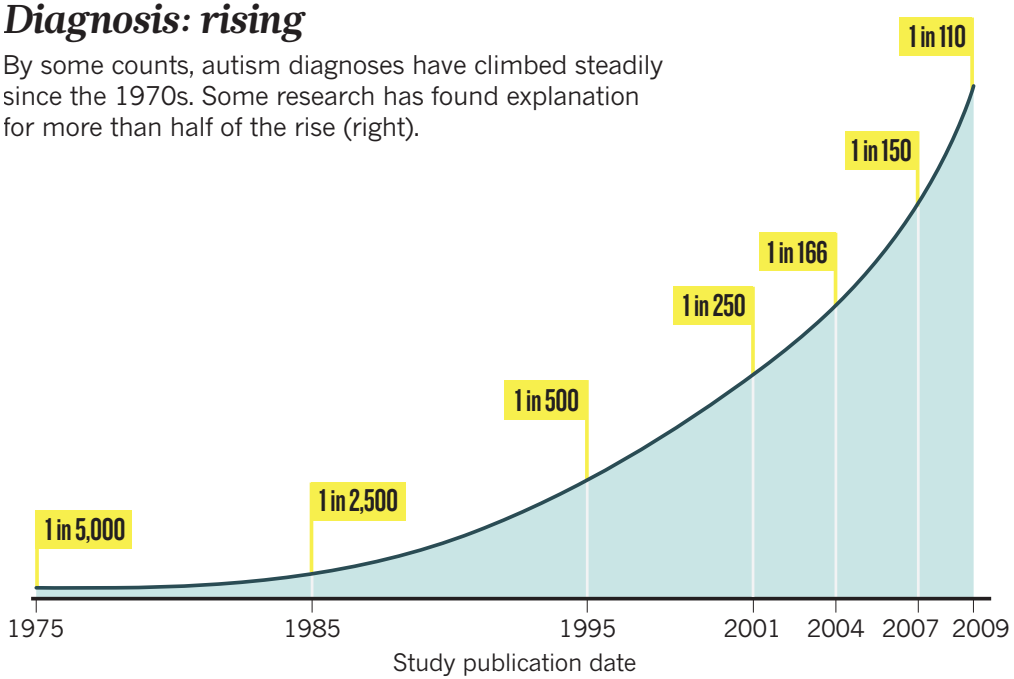
Sensitivity vs. Specificity

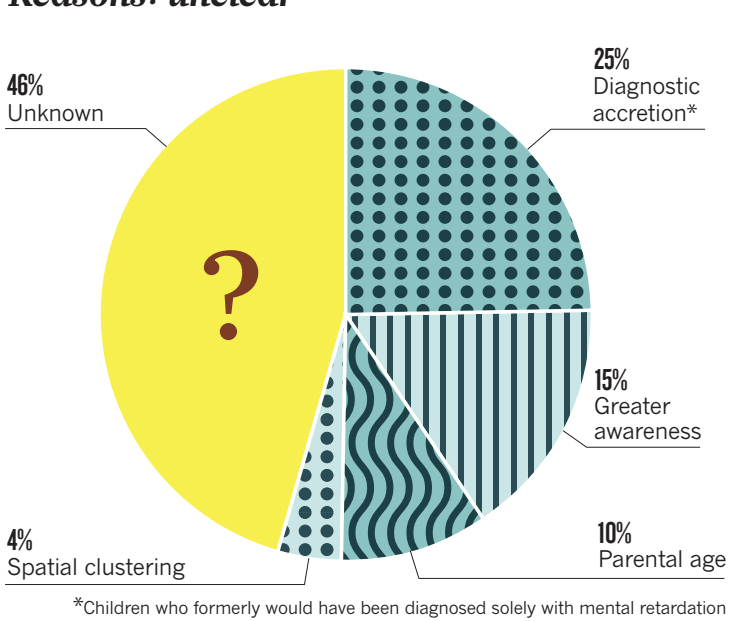
Autism vs. “neurotypical”

Autism vs. other psychiatric illness

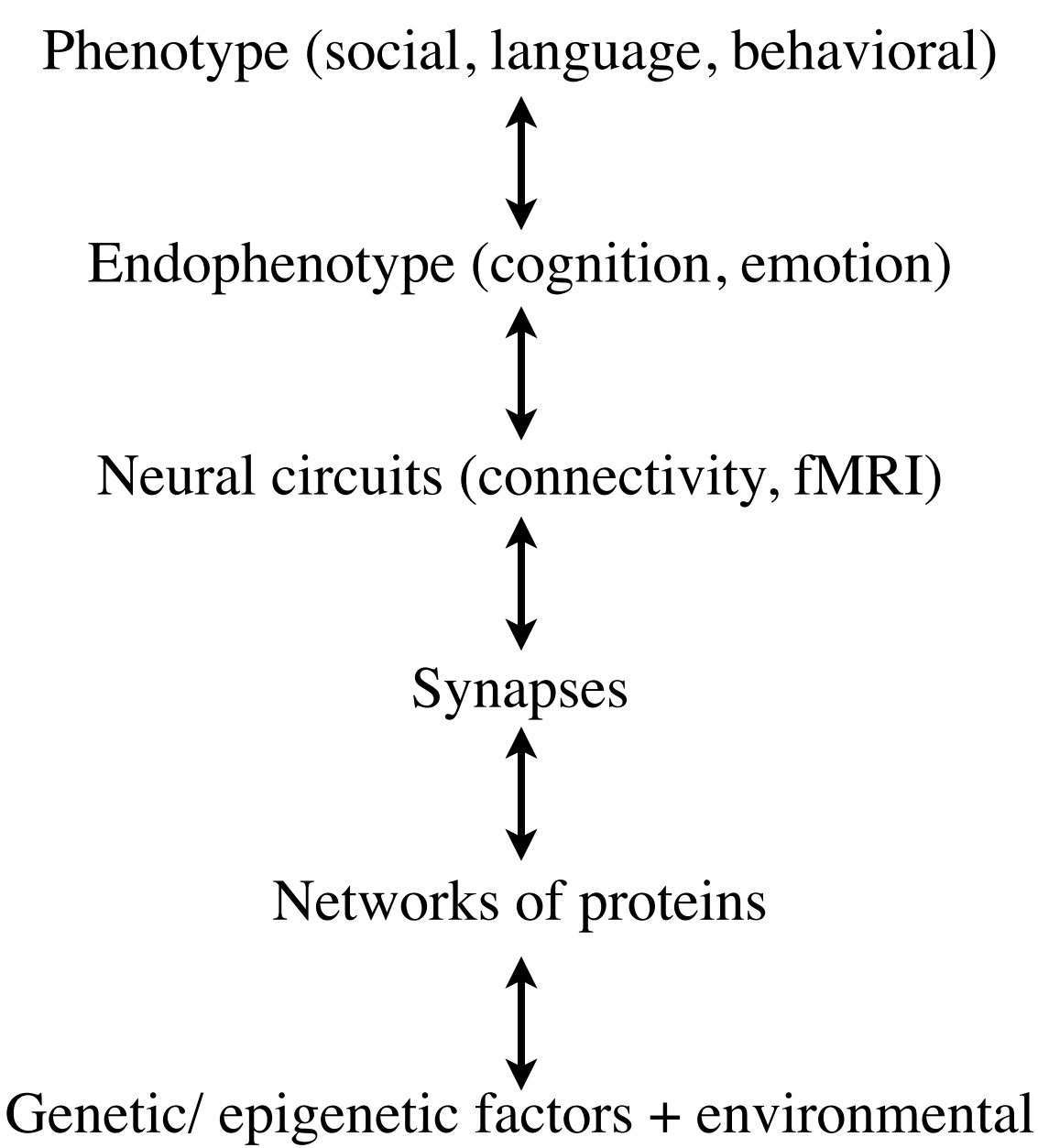
Low-functioning vs. high-functioning

- incidence: close to 1% for ASD





Nature, 3 Nov. 2011


Phenotype (social, language, behavioral)
Endophenotype (cognition, emotion)
Neural circuits (connectivity, fMRI)
Synapses
Networks of proteins
Genetic/ epigenetic factors + environmental

Autism is a pervasive developmental disorder

-early onset (2 years of age for diagnosis)

-lifelong

Autism runs in families

-very high heritability (0.8-0.9 perhaps)

-mostly males

-there is a spectrum (Asperger's, autism, etc.)

Autism is psychiatrically defined illness

-diagnosis on behavioral criteria only

-but there are many biological "markers"

Children with autism have larger brains

Heritability of Autism

-MZ twins: 70% autism, 90% ASD

-DZ twins: 5%, 10%

- more frequent in males than females (4:1; 10:1 for high-functioning)

Table 1 | **Examples of proposed biomarkers for autism**

Biomarker type	Sample/measure	Refs
Gene expression profile	Blood samples	9
Proteomic profile	Serum samples	62
Metabolomic profile	Urine samples	63
Head size	Head circumference trajectory	64
Brain size and structure	MRI, DTI	13
Brain function	Functional MRI, EEG, ERPs	20
Eye movement	Looking measures, saccadic reaction time	21

DTI, diffusion tensor imaging; EEG, electroencephalography; ERPs, event-related potentials.

Nature Reviews Neuroscience (2011) 12:603

Genes that contribute to autism:

-synaptic proteins: neuroligins, neurexins

-cell adhesion molecules

-receptors

Related Disorders:

ASD: autism, Asperger Syndrome, PDD-NOS

Fragile X: (FMR-1 gene triplet repeats)

--as high as 40% of FRAX may have autism

--but <5% of autism have FRAX

Tuberous Sclerosis

--as high as 20-60% have autism

--but <3% of people with autism have TSC

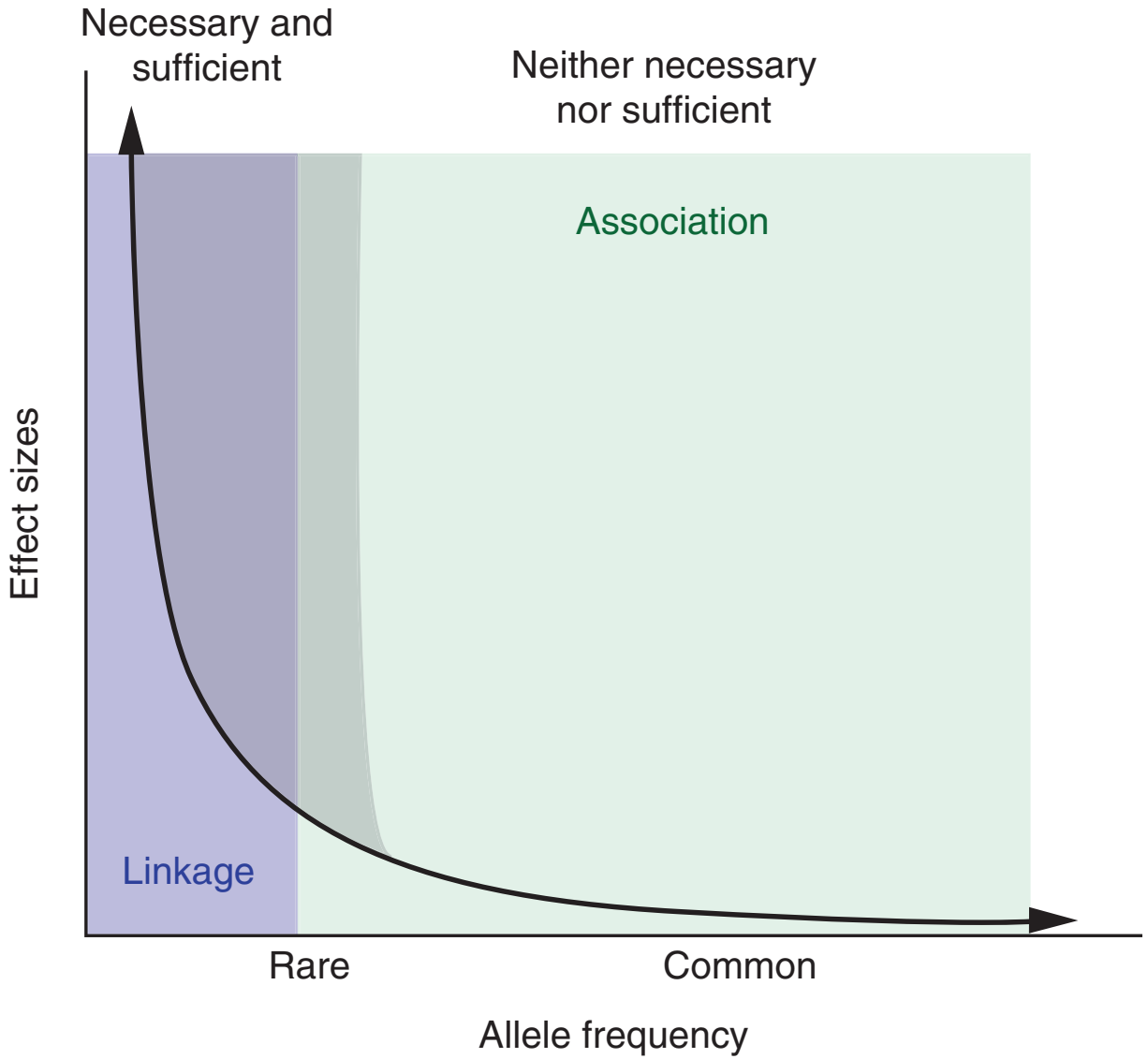
Table 1 | **ASD-related syndromes**

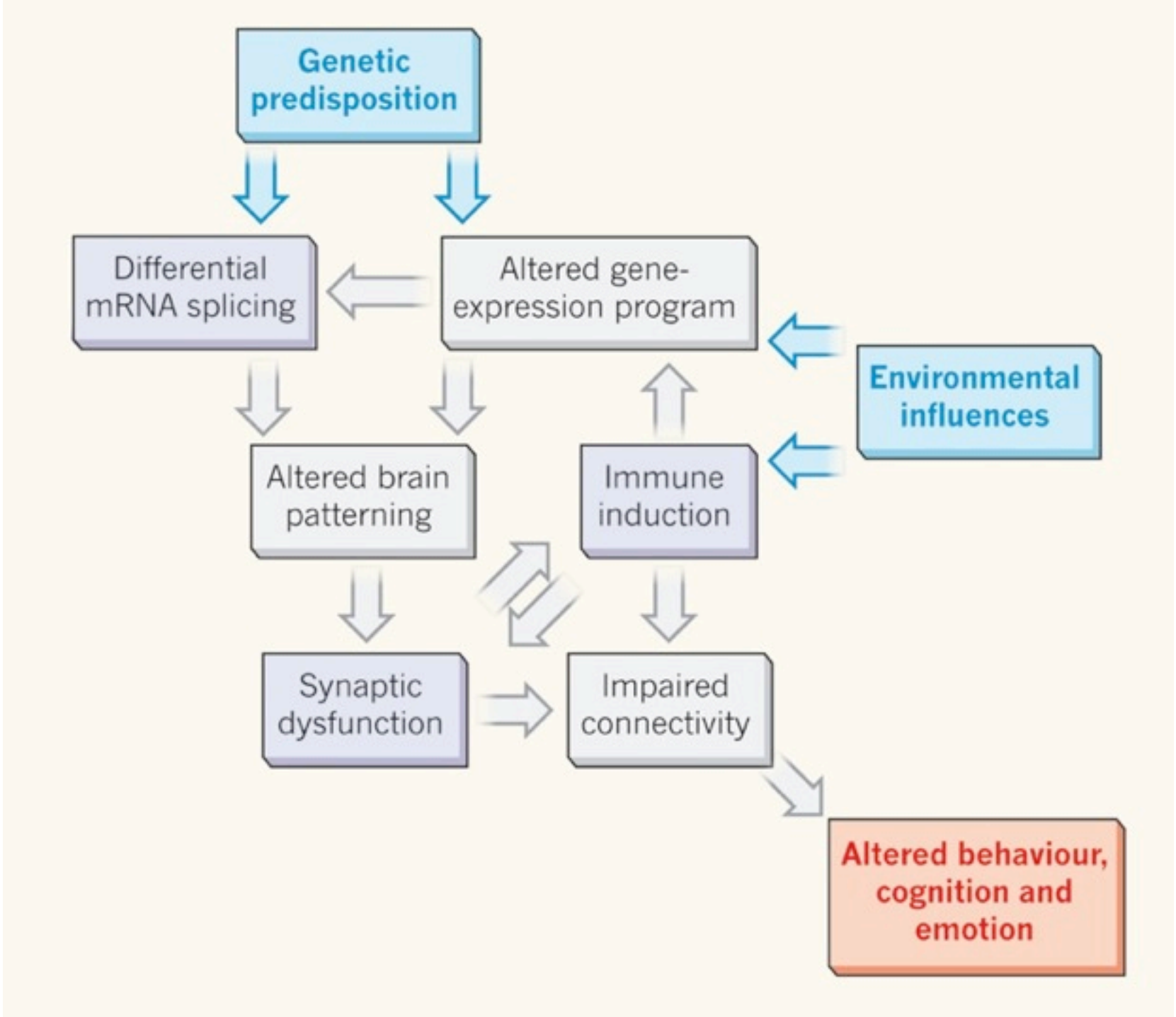
Syndrome	Gene(s) associated with the syndrome	Proportion of patients with the syndrome that have an ASD	Proportion of patients with an ASD that have the syndrome	Refs
15q duplication — Angelman syndrome	*UBE3A* (and others)	>40%	1–2%	101–103
16p11 deletion	Unknown	High	~1%	20, 35, 44
22q deletion	*SHANK3*	High	~1%	21, 22, 104
Cortical dysplasia-focal epilepsy syndrome	*CNTNAP2*	~70%	Rare	37
Fragile X syndrome	*FMR1*	25% of males; 6% of females	1–2%	105
Joubert syndrome	Several loci	25%	Rare	106
Potocki–Lupski syndrome	Chromosome position 17p11	~90%	Unknown	107
Smith–Lemli–Optiz syndrome	*DHCR7*	50%	Rare	108
Rett syndrome	*MECP2*	All individuals have Rett syndrome	~0.5%	109
Timothy syndrome	*CACNA1C*	60–80%	Unknown	24
Tuberous sclerosis	*TSC1* and *TSC2*	20%	~1%	110

The rates quoted in the table depend on the population that is being evaluated. For example, rates are higher in individuals from simplex families compared with multiplex families, and are higher in dysmorphic and mental retardation populations compared with idiopathic populations. 'High' is used for syndromes in which no good estimates exist (that is, only a handful of individuals with the syndrome in question have been identified). It should also be noted that none of the studies cited here indicates that assessment for the autism spectrum disorder (ASD) was performed blind to a patient's primary diagnosis. An expanded version of the table with additional variables can be found in Supplementary information S1 (table). *CACNA1C*, calcium channel voltage-dependent L type alpha 1C subunit; *CNTNAP2*, contactin associated protein-like 2; *DHCR7*, 7-dehydrocholesterol reductase; *FMR1*, fragile X mental retardation 1; *MECP2*, methyl CpG binding protein 2; *SHANK3*, SH3 and multiple ankyrin repeat domains 3; *TSC1*, tuberous sclerosis 1; *TSC2*, tuberous sclerosis 2; *UBE3A*, ubiquitin protein ligase E3A.

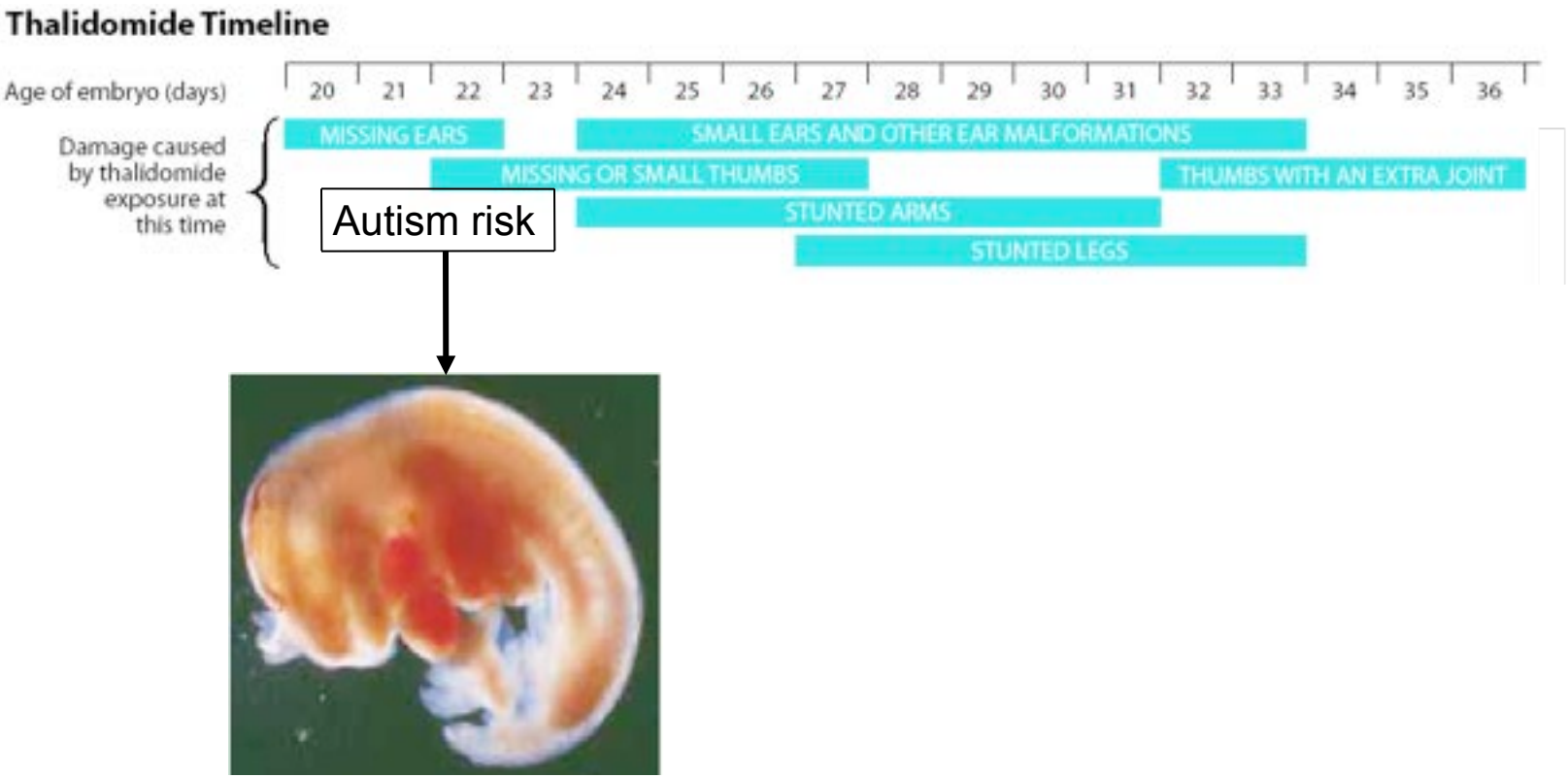
- Autism is a primarily multigenic, genetically heterogeneous disease, with each gene contributing a small amount of risk. It does not run in families in either a dominant or recessive pattern. (But it DOES run in families).

- In addition, several rare, single gene mutations and chromosomal abnormalities can strongly increase risk for autistic features: Fragile X (FRAXA), tuberous sclerosis (TSC), Smith-Lemli-Opitz syndrome (dehydrocholesterol reductase), Rett (MeCP2), Prader-Willi/Angelman (15q11-g13 breaks). Only a small percentage of autism can be attributed to these.


Necessary and sufficient
Neither necessary nor sufficient
Association
Linkage
Effect sizes
Rare
Common
Allele frequency

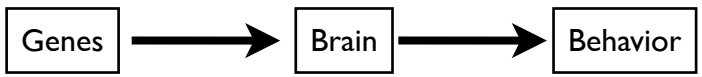

Genetic predisposition
Differential mRNA splicing
Altered gene-expression program
Environmental influences
Altered brain patterning
Immune induction
Synaptic dysfunction
Impaired connectivity
Altered behaviour, cognition and emotion

Autism can arise very early in development

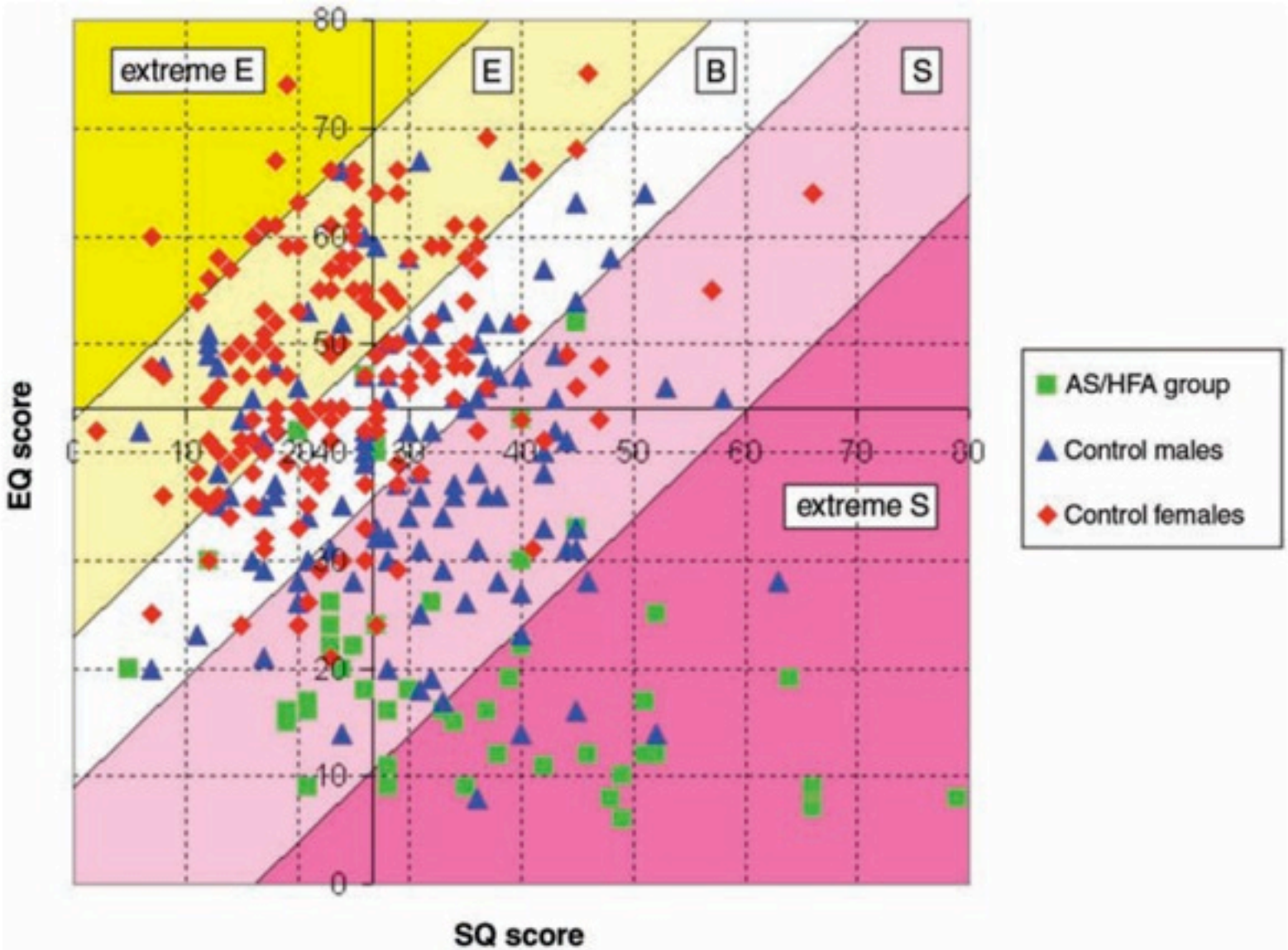


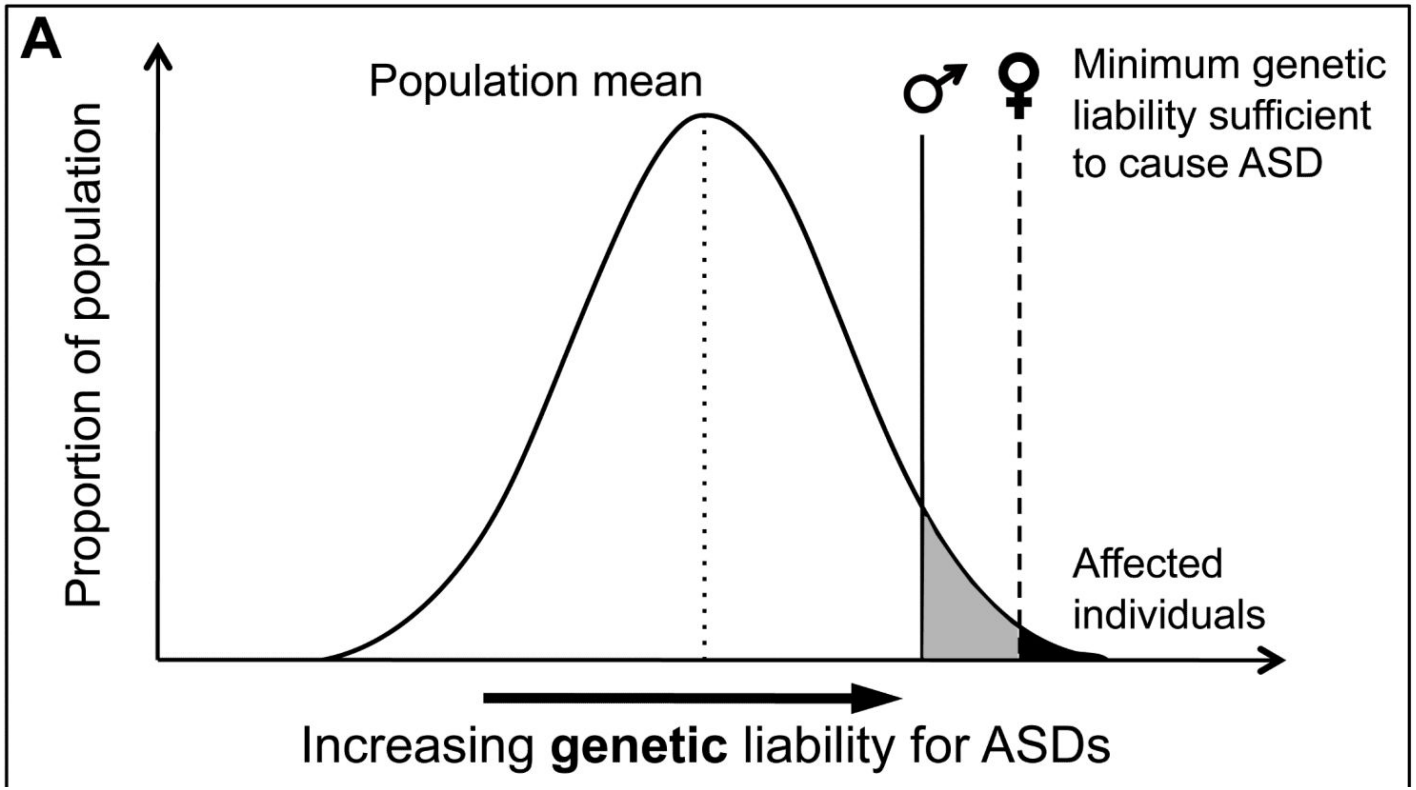
Rodier, 2000

What causes Autism?

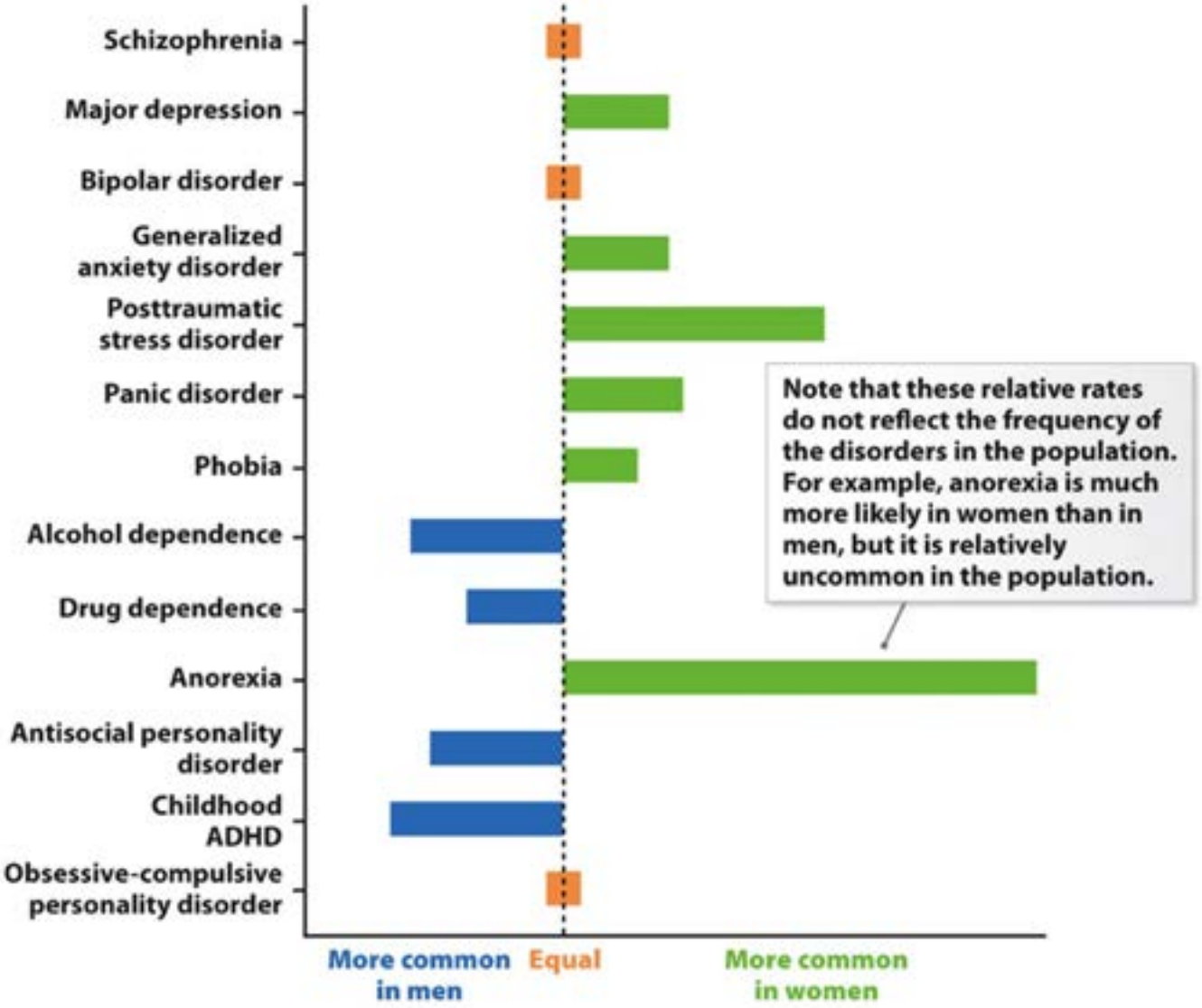

Genes
Brain
Behavior

Simon Baron-Cohen's
"Extreme male brain hypothesis"





Werling & Geschwind, Curr Opin Neurol (2013) 26: 146.



Psychological Science, 4/e Figure 14.10
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Risk factors	Men	Women	*P*
Hypertension	563 (66.39)	486 (76.42)	<0.001
Diabetes	224 (26.42)	191 (30.03)	0.125
Atrial fibrillation	137 (16.16)	120 (18.87)	0.172
Dyslipidemias	193 (22.76)	193 (30.35)	0.001
Obesity	79 (9.32)	117 (18.40)	<0.001
Intracranial artery stenosis	196 (23.11)	111 (17.45)	0.008
Current smoking	251 (29.60)	83 (13.05)	<0.001
Alcohol consumption	103 (12.15)	3 (0.47)	<0.001

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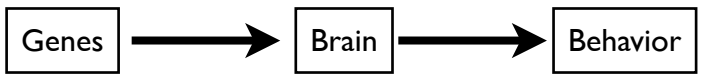
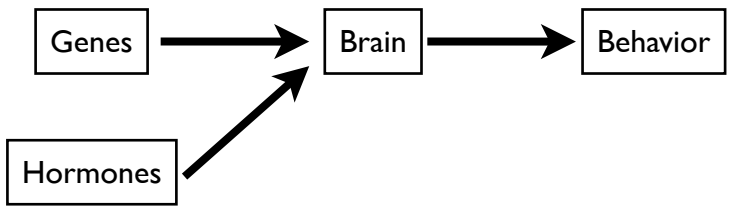
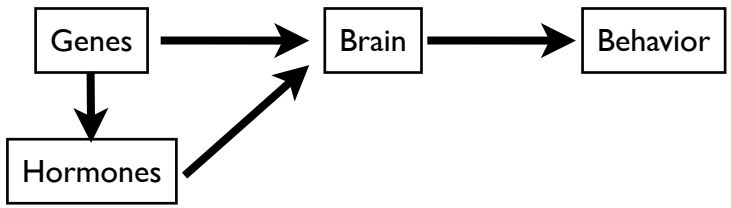
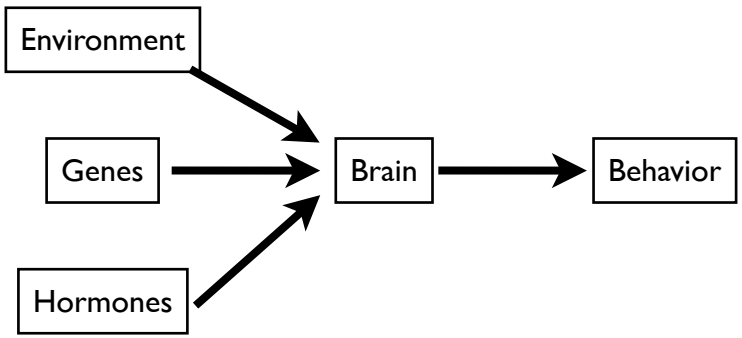
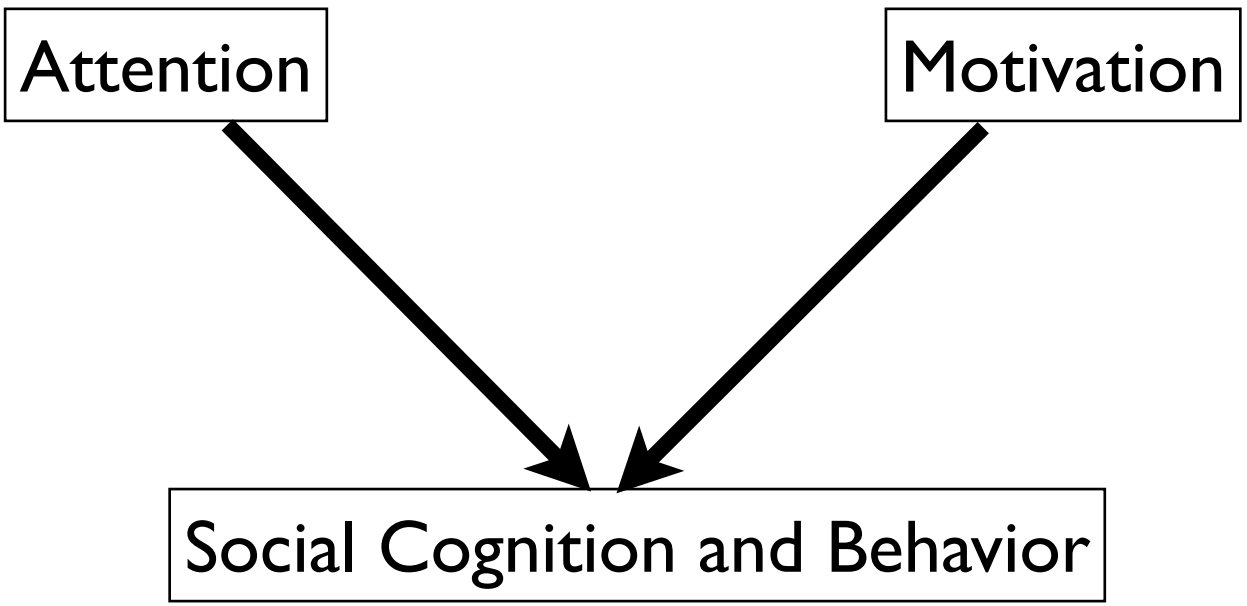
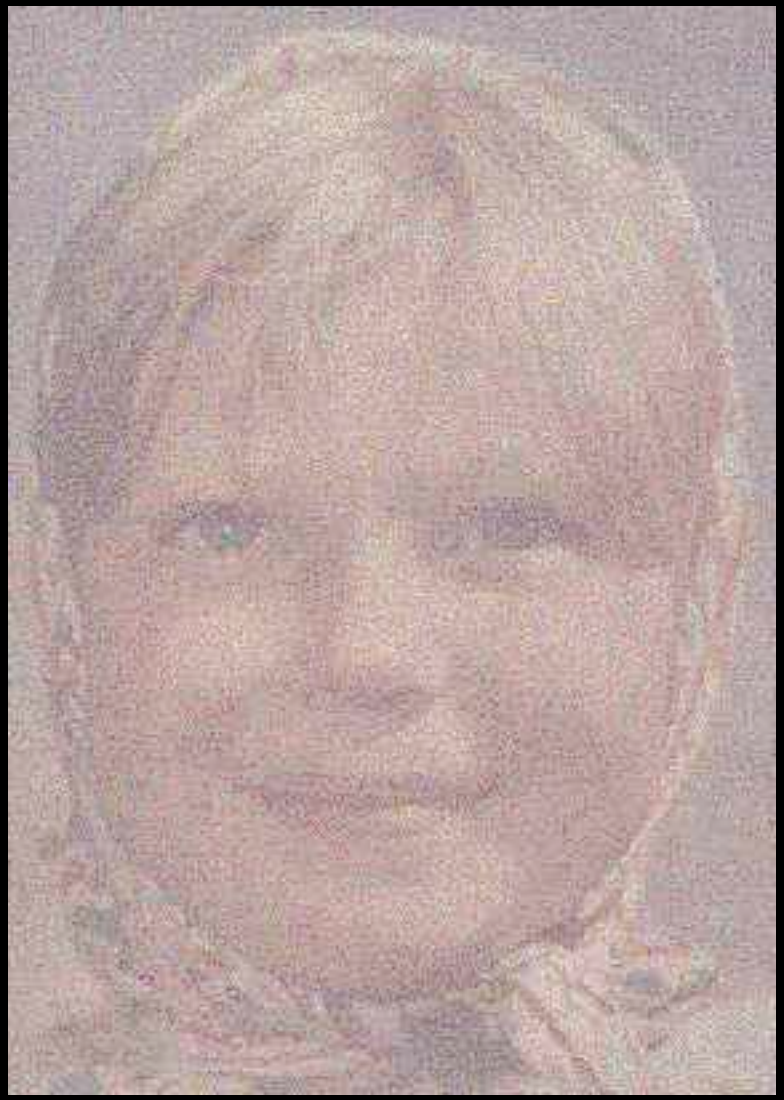

Genes
Brain
Behavior


Genes
Brain
Behavior
Hormones


Genes
Brain
Behavior
Hormones


Environment
Genes
Hormones
Brain
Behavior


Attention
Motivation
Social Cognition and Behavior



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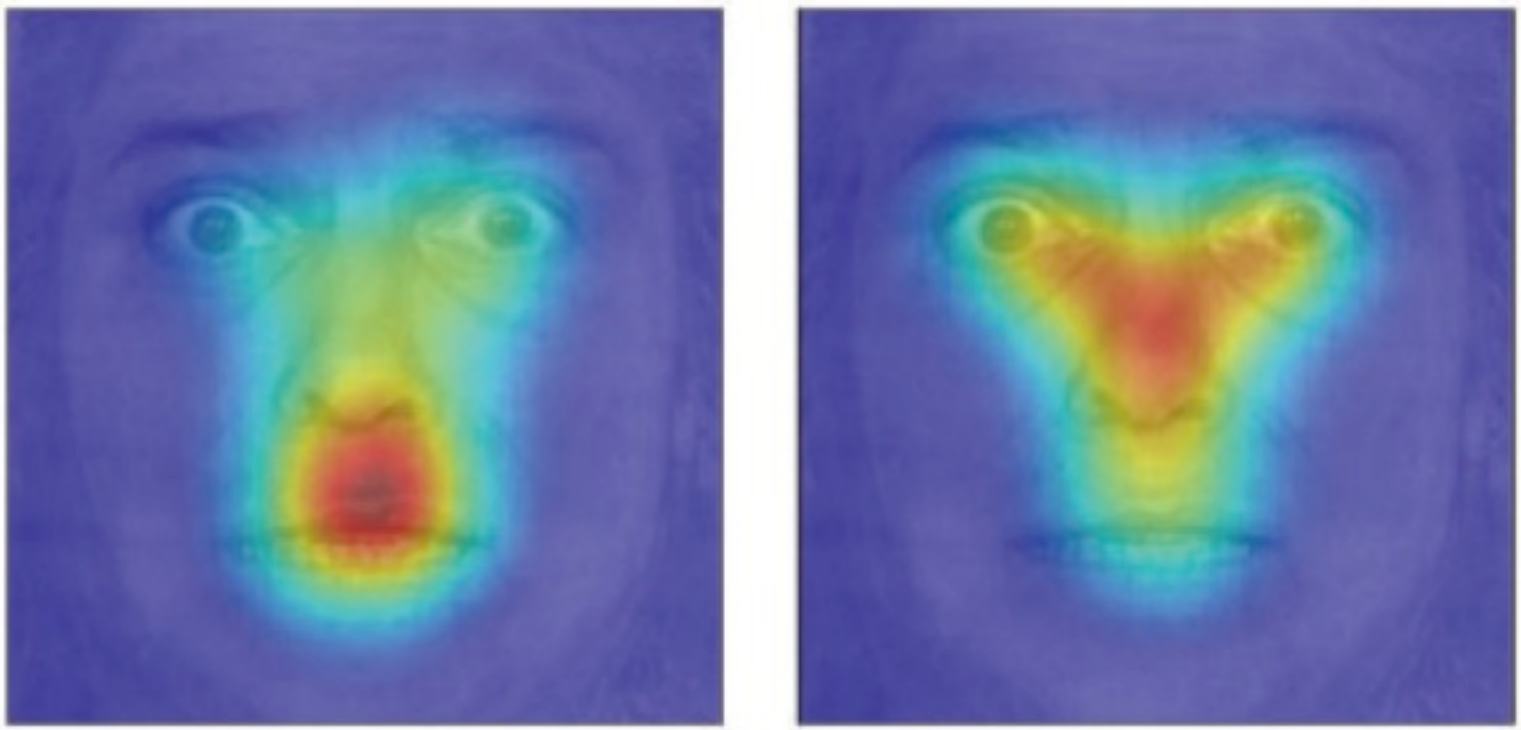
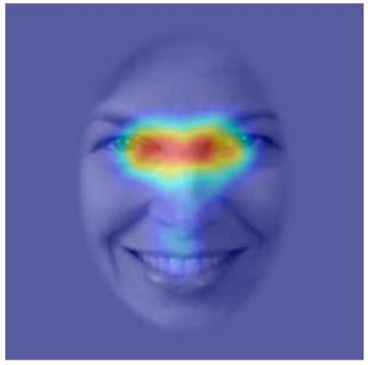


Autism

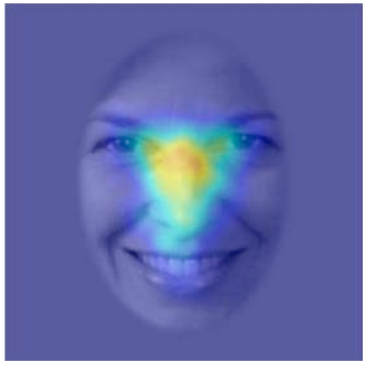
Control

Comparisons between Autism and Amygdala Lesions

Controls

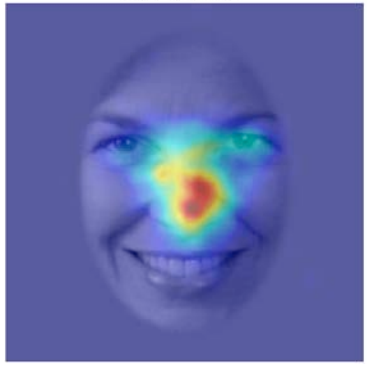


Autism



Control - Autism

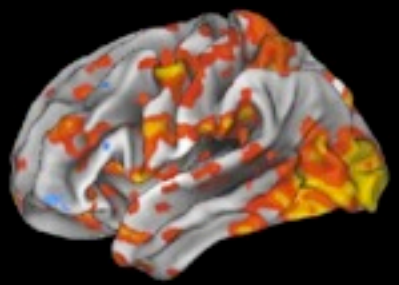
SM
(amygdala lesion)



Dynamic, semi-naturalistic/semi-realistic stimuli

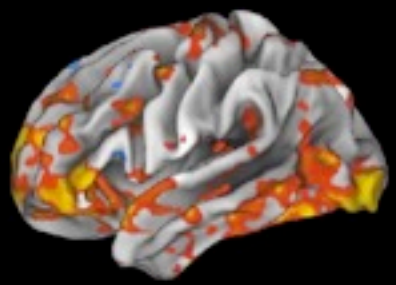
The Office, © NBC Universal

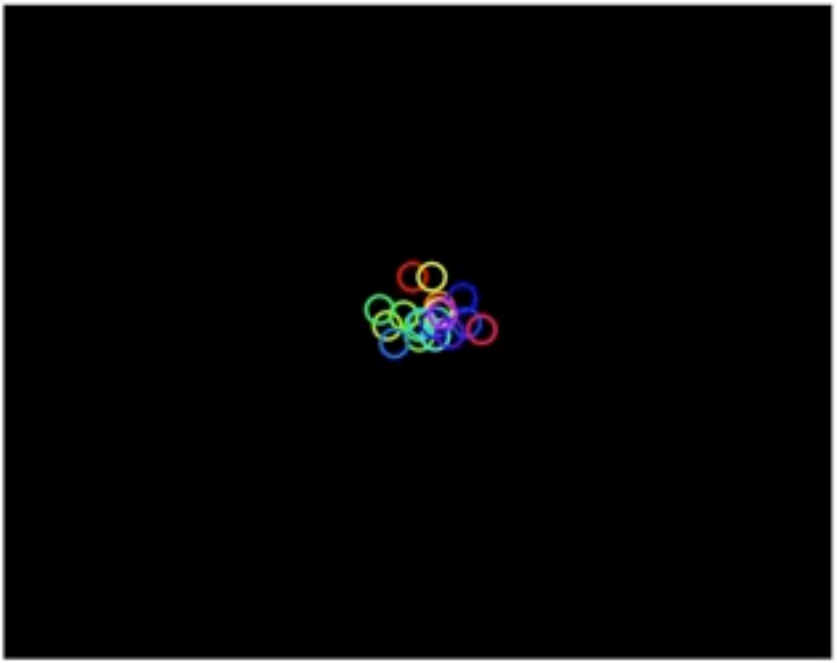
Control average



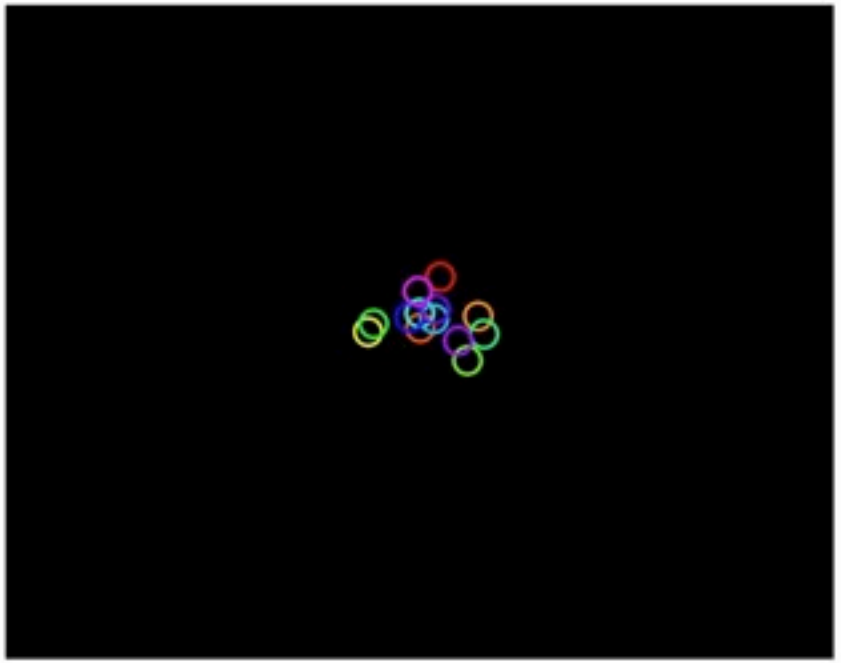
Time = 1min45s

ASD average



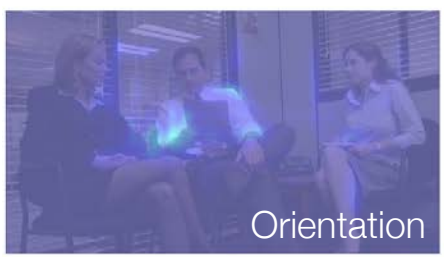


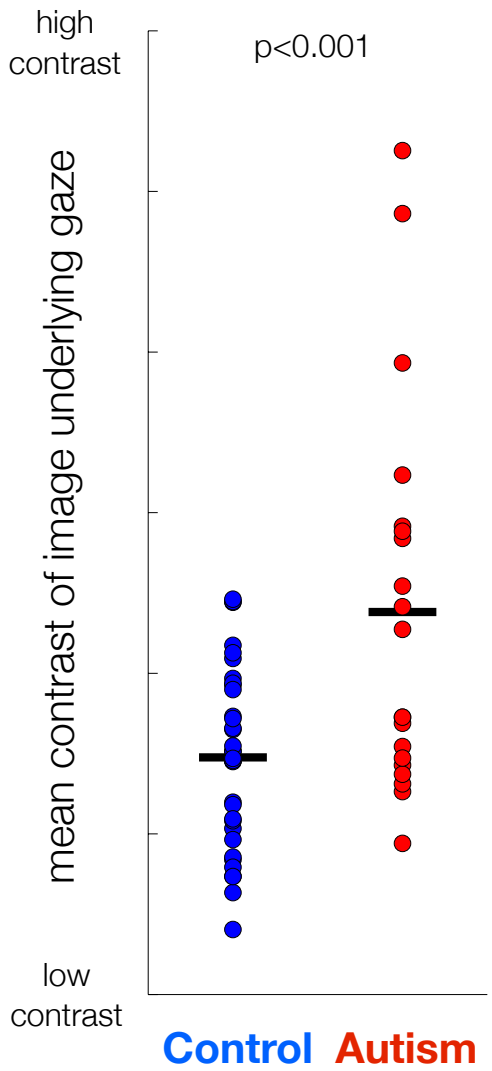
Controls

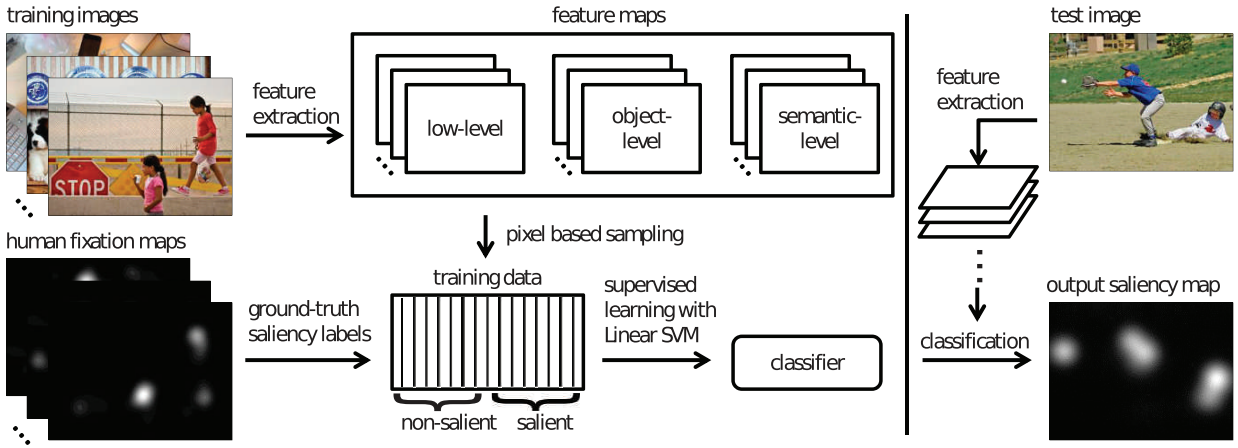


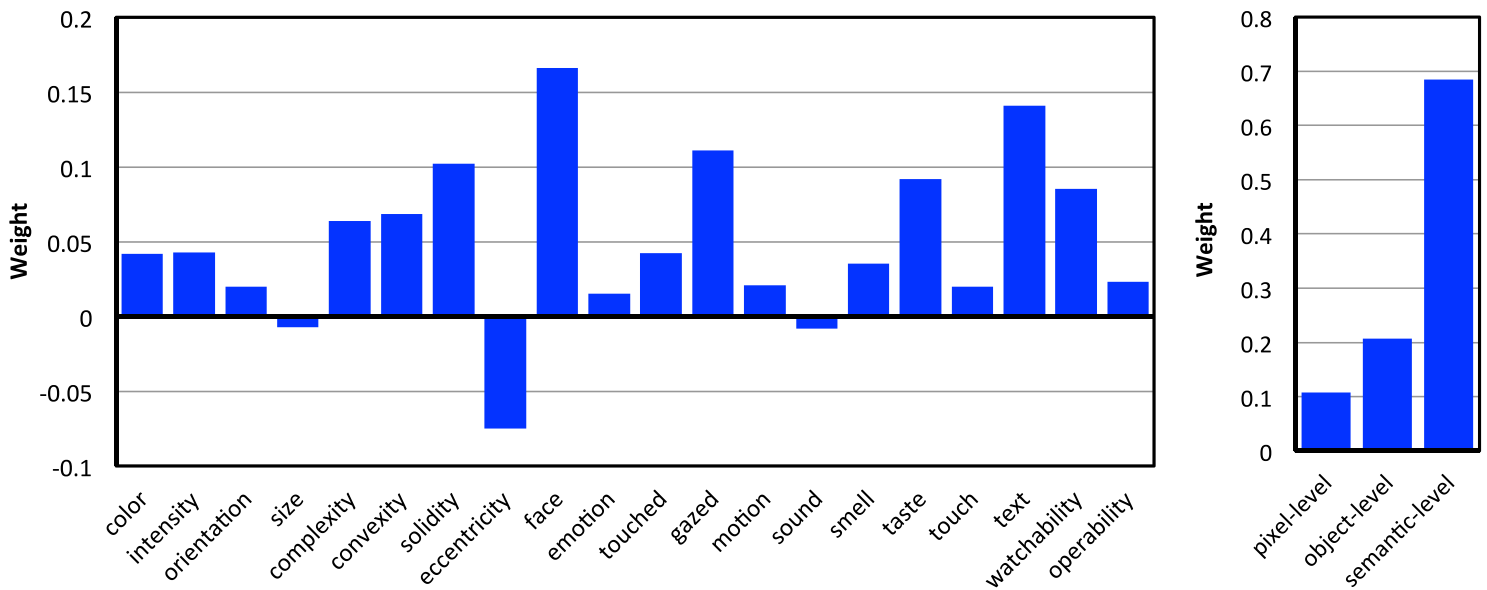
ASD

Low-level visual features - Image saliency









Xu, J. et al. (2014). *Journal of Vision* 14: 1-20

Neuropathology:

- Amygdala (post-mortem, structural, fMRI, lesions)
- Hippocampus (post-mortem, structural)
- Brainstem nuclei (structural)
- Cerebellum (post-mortem, structural)
- Cortical regions (structural and fMRI)
- White matter (structural and DTI)

Current Directions

- combine genotyping with structural, diffusion and functional MRI in humans

- do studies in very young infants

- animal models

Autistic mice??

- emotion/anxiety: response to stress
- social: social preference test
- language: ultrasonic vocalization
- stereotypies: grooming

Table 1 | **Examples of autism-relevant behaviours in genetic mouse models of autism spectrum disorders**

Mouse model	Genetic characteristics	Behavioural phenotypes relevant to the symptoms of autism*
Nlgn4	Null mutation in the murine orthologue of the human *NLGN4* gene[43]	• Reduced reciprocal social interactions[43] • Low sociability[43] • Lack of preference for social novelty[43] • Reduced ultrasonic vocalizations[43]
Nlgn3	Homozygous mutation of humanized R451C mutation of the *Nlgn3* gene[44,45]	• No genotype differences in reciprocal social interactions[44,45] • No genotype differences in sociability[44,45] • No genotype differences in preference for social novelty[44] • Reduced ultrasonic vocalizations[44]
	Null mutation in the murine orthologue of the human *NLGN3* gene[41]	• No genotype differences in reciprocal social interactions[41] • Reduced preference for social novelty[41]
Neurexin 1α	Null mutation in the murine *neurexin 1α* generated by deleting the first exon of the gene[46]	• No genotype differences in reciprocal social interactions[46] • No genotype differences in sociability[46] • Impaired nest-building behaviour[46] • Increased repetitive self-grooming[46]
Nlgn1	Null mutation in the murine orthologue of the human *NLGN1* gene[47]	• No genotype differences in reciprocal social interactions[47] • No genotype differences in sociability[47] • No genotype differences in preference for social novelty[47] • Impaired nest-building behaviour[47]
Pten	Conditional null mutation, inactivated in neurons of the cortex and hippocampus, mouse orthologue of the human *PTEN* gene[68]	• Reduced reciprocal social interactions[68] • Low sociability[68] • Impaired nest-building behaviour[68] • Impaired social recognition[68]
	Pten haploinsufficent mutant line in which exon 5, and thus the core catalytic phosphatase domain, is deleted[48]	• Low sociability in females[48]
En2	Null mutation in the murine orthologue of the human *EN2* gene[49,50]	• Reduced reciprocal social interactions[49] • Increased repetitive self-grooming[49] • No genotype differences in sociability, confounded by low activity levels[50]
15q11–13	Duplication in the genomic region on the mouse chromosome 7 homologous to the human genomic region 15q11–13 (REF. 29)	• Low sociability[29] • Ultrasonic vocalizations elevated in pups and reduced in adults[29] • Impaired reversal learning[29]
17p11.2	Duplication in the genomic region of murine chromosome 11 homologous to the human genomic region 17p11.2 (REF. 51)	• Low sociability[51] • No genotype differences in preference for social novelty[51] • Impaired nest-building behaviour[51]
Gabrb3‡	Null mutation in the murine orthologue of the human *GABRB3* gene[52]	• Low sociability‡ (REF. 52) • Lack of preference for social novelty‡ (REF. 52) • Repetitive stereotyped circling patterns‡ (REF. 52) • Impaired nest-building behaviour‡ (REF. 52)

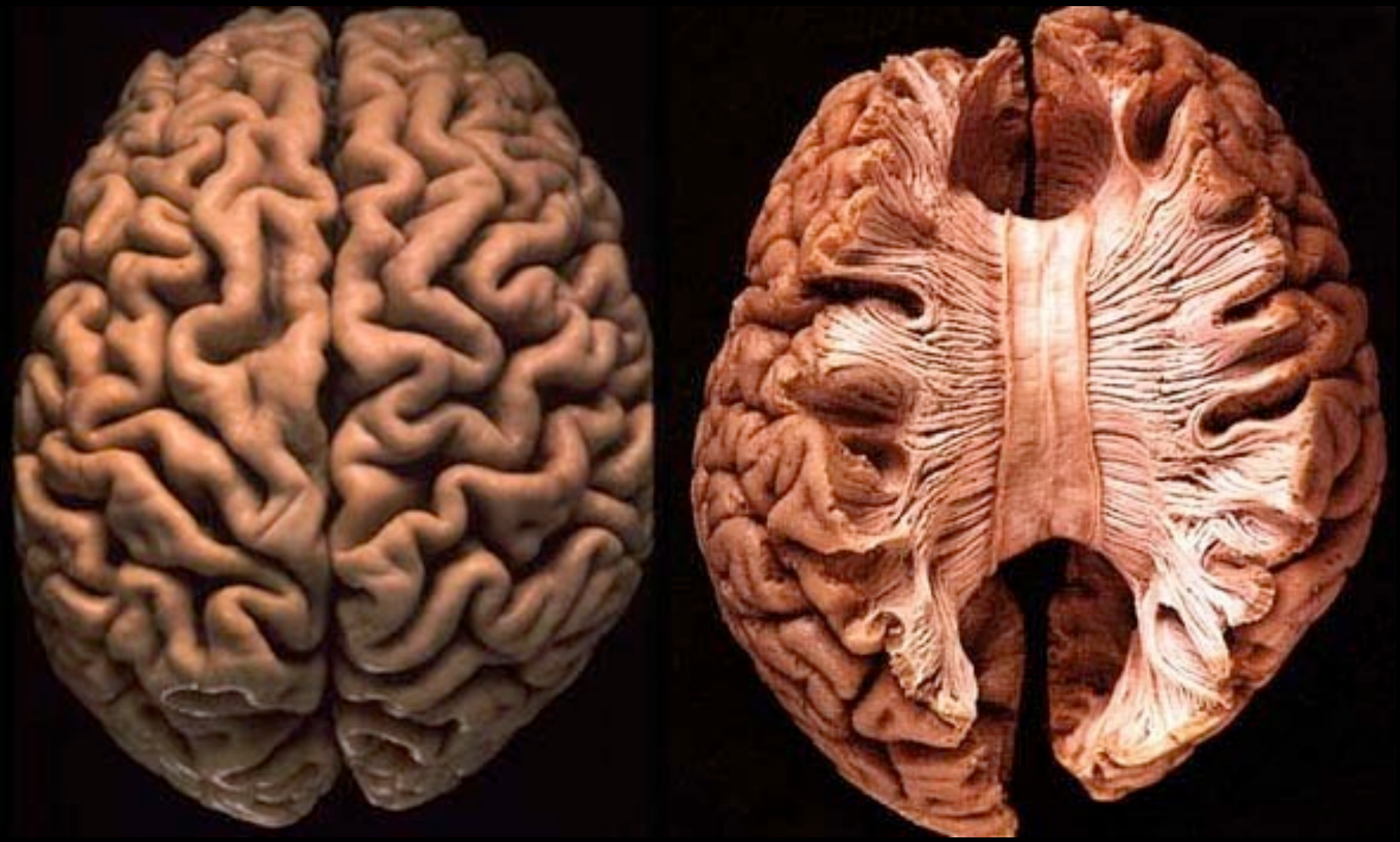
Maternal influenza infection mouse model

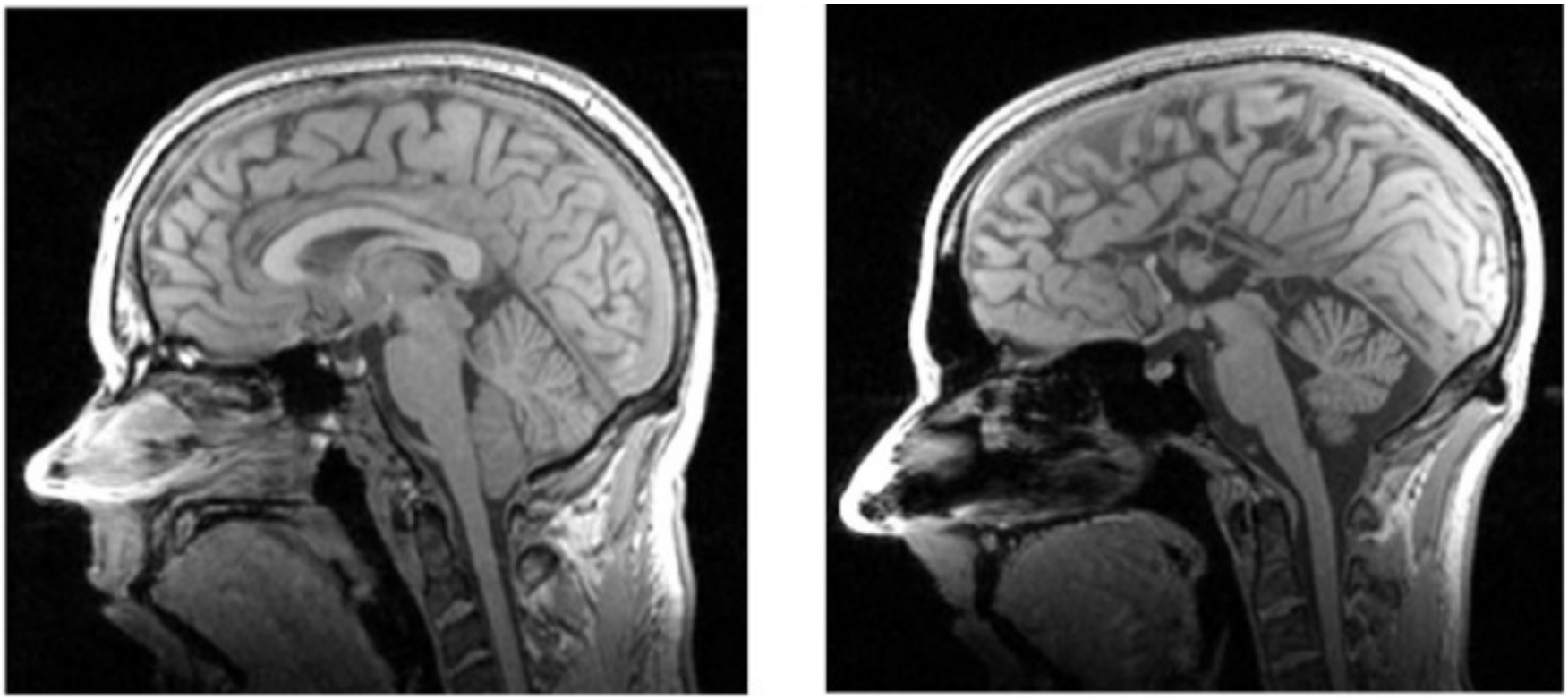
Nasal application of human influenza virus at mid-pregnancy

Lethargic
Ungroomed, ruffled fur
Hunched posture

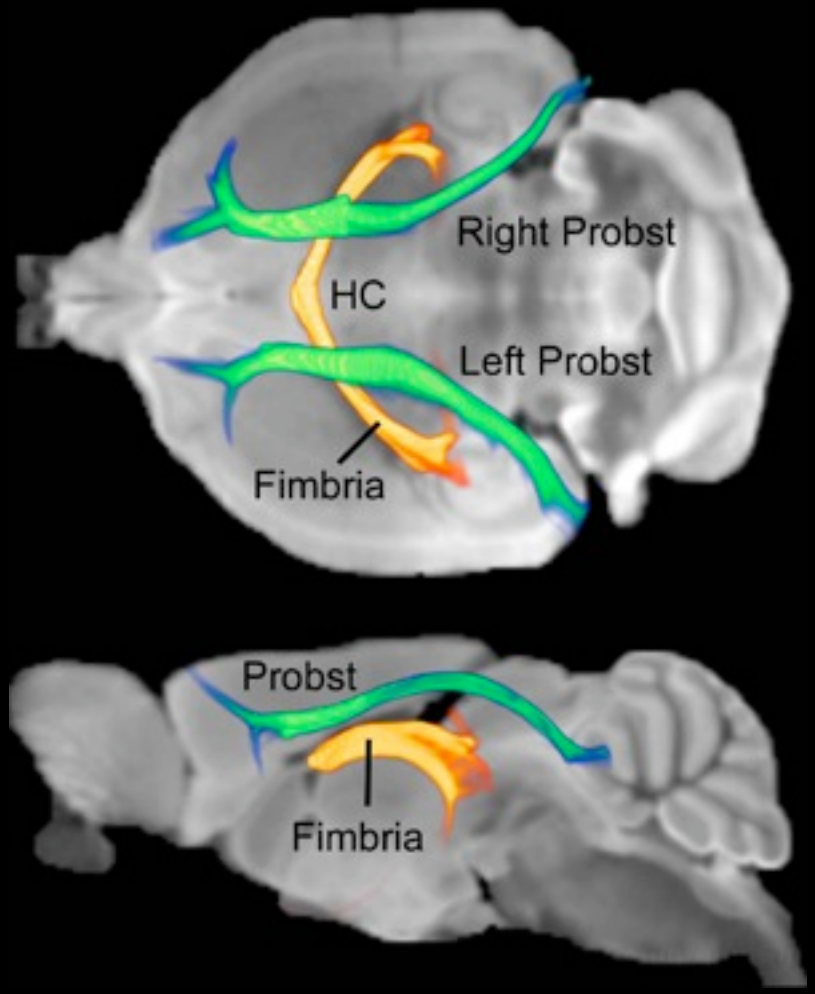
No detectable virus in pups or in fetal brain

Other human diseases relevant to autism





Agenesis of the Corpus Callosum

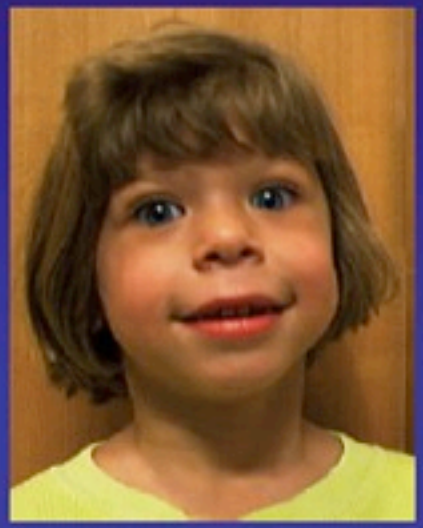


Tractography of the brain of mouse strain BTBR, which has agenesis of the callosum and is a mouse model of autism.

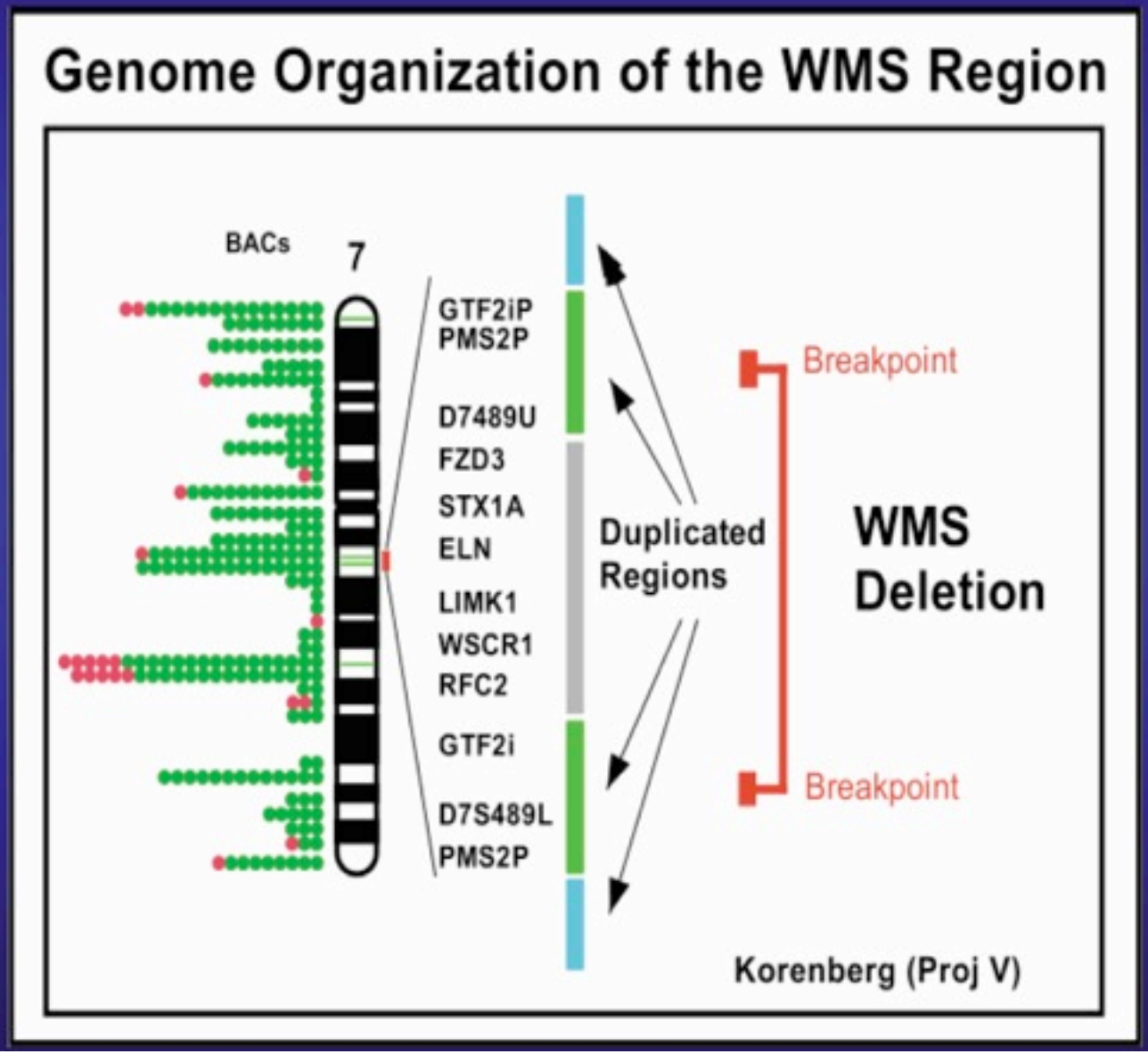
Caltech Brain Imaging Center

Williams Syndrome

Faces of Children with Williams Syndrome



Molecular Genetics of Typical Deletions in WMS:
(hemizygous deletion on chromosome 7, band 7q11.2)



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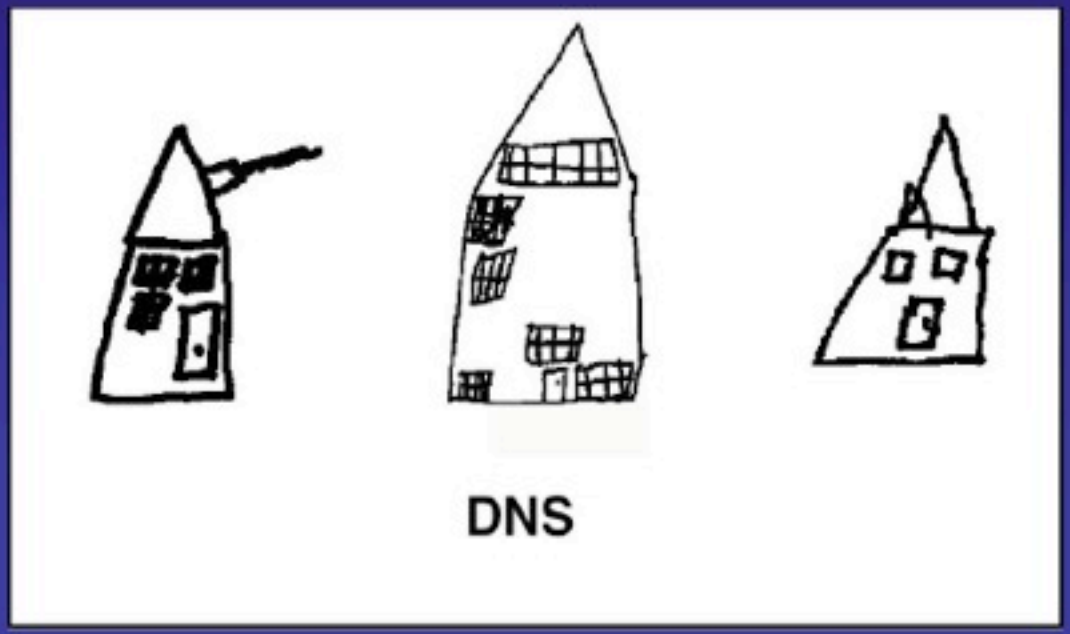
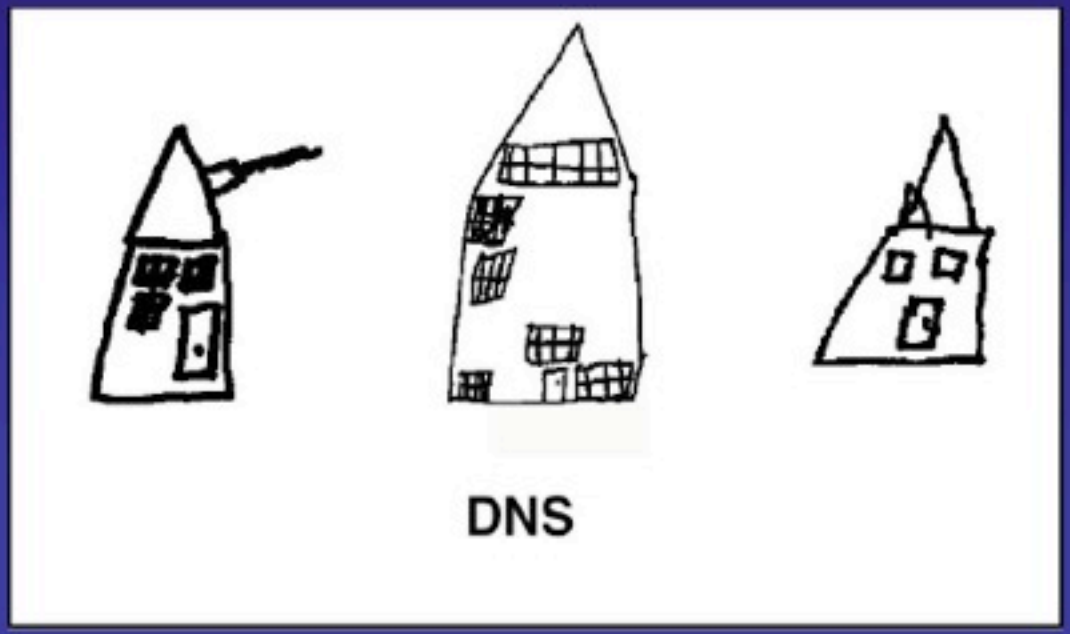
DNS Age 10: Mom wash dishes. A bowl fell. Boy slips, boy pushed. Boy helps mom with dishes. Mom big mess in water. Pushing. (Examiner: Can you tell me anything else about the picture?) (*shakes head*)

Examiner: I want you to look at the picture and tell me everything that is going on.

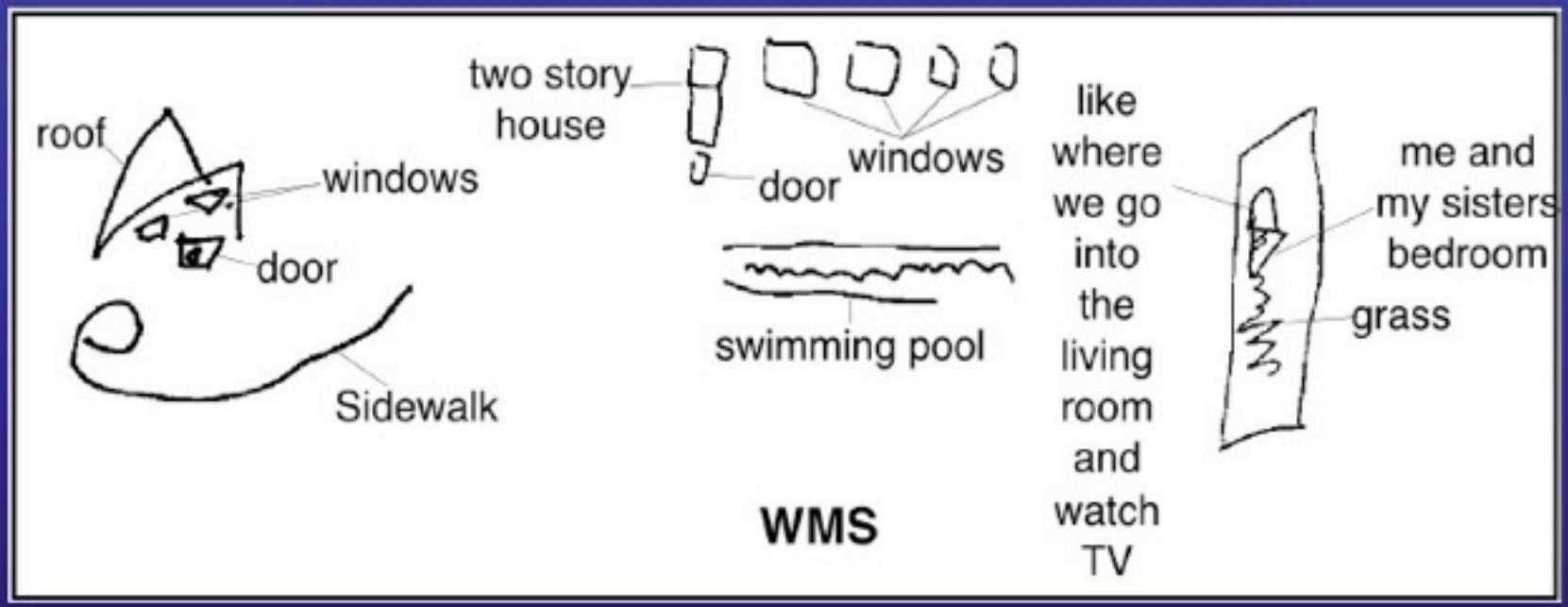
DNS Age 10: Mom wash dishes. A bowl fell. Boy slips, boy pushed. Boy helps mom with dishes. Mom big mess in water. Pushing. (Examiner: Can you tell me anything else about the picture?) (*shakes head*)

WMS Age 10: (*Laughs*). Oh no. The Mommy left the tap on (pointing to the water). And the boy is trying to get a cookie but the chair is tipping over. (*In a high voice, as if addressed to the mother*) Mom, won't you save her boy? (*Returning to a normal tone*) Her son and her daughter. Oh, there's going to be a flood on the floor. The boy's in the cookies. Maybe it's after supper. Oh, the mommy is drying the towel. Poor boy, he could get hurt and break his arm. Poor boy, oh poor thing.

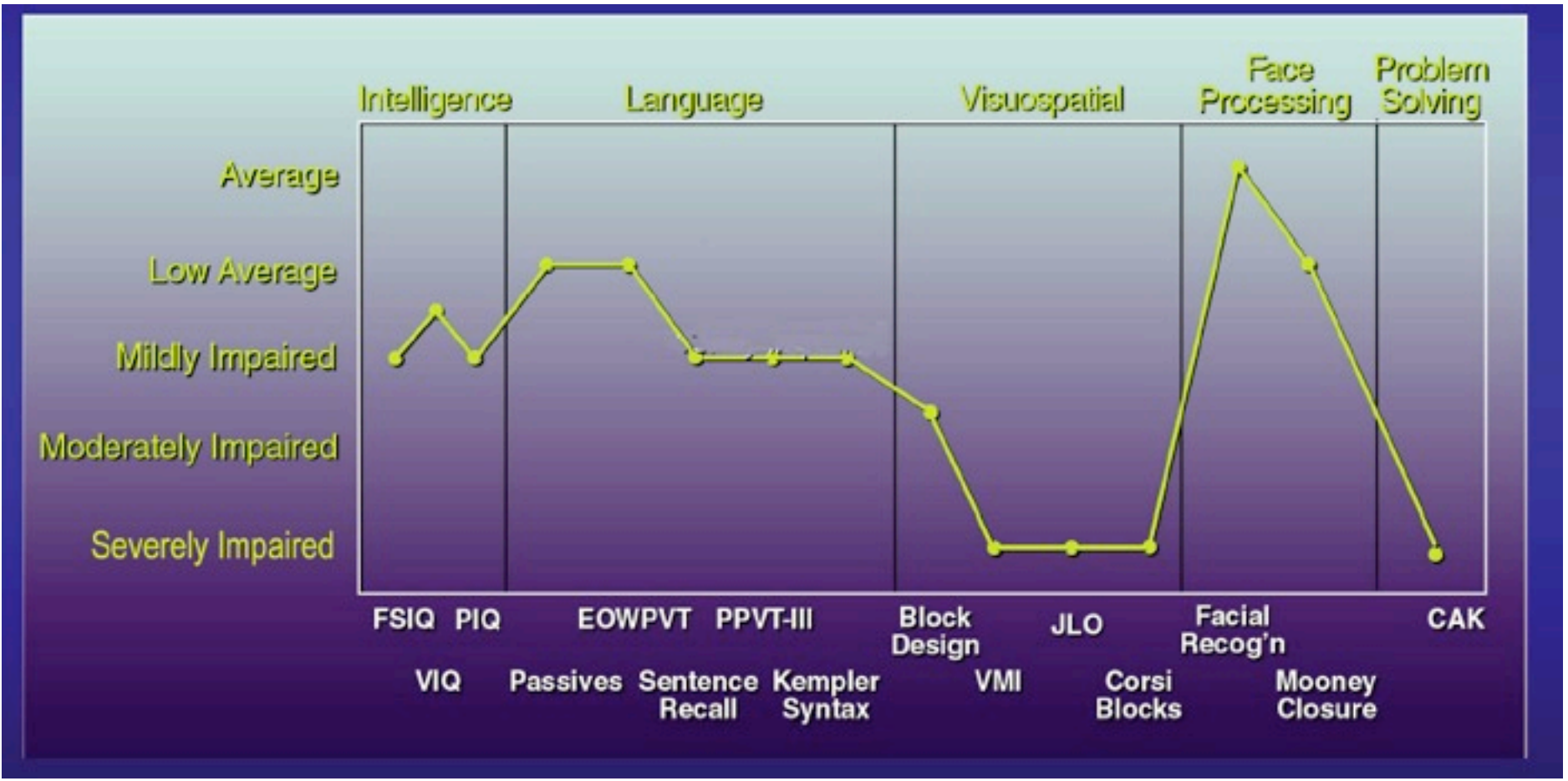

DNS



DNS


roof
windows
door
Sidewalk
two story house
door
windows
swimming pool
like where we go into the living room and watch TV
me and my sisters bedroom
grass

WMS


Intelligence
Language
Visuospatial
Face Processing
Problem Solving
Average
Low Average
Mildly Impaired
Moderately Impaired
Severely Impaired
FSIQ
PIQ
VIQ
EOWPVT
PPVT-III
Passives
Sentence Recall
Kempler Syntax
Block Design
JLO
VMI
Corsi Blocks
Facial Recog'n
Mooney Closure
CAK