NEUROLOGY AND AUTISM: WHAT IS THE ROLE OF THE PEDIATRIC NEUROLOGIST?

DAY BREEN, MD

PEDIATRIC NEUROLOGY & NEURODEVELOPMENTAL DISABILITIES

CHILDREN'S HOSPITAL AT ERLANGER

What Does a Pediatric Neurologist Do?

- Encompasses disorders of the brain, spinal cord, peripheral nerve and muscle affecting infants, children and adolescents

What Does a Pediatric Neurologist Do?

- Seizures & epilepsy
- Muscle problems which may cause weakness, such as: muscular dystrophy or neuropathy
- Headaches, including migraines and concussions
- Behavioral disorders, including attention-deficit/hyperactivity disorder (ADHD), tics and Tourette Syndrome, and sleep problems
- Autism
- Developmental disorders, including cerebral palsy, delayed speech, delayed motor milestones, and coordination issues
- Intellectual disability
- Congenital malformations, which are problems in how the brain forms or develops
- Stroke and traumatic brain injury (TBI)
- Genetic conditions that affect the nervous system
- Autoimmune problems that impact the brain and spinal cord (such as multiple sclerosis)
- Infections or inflammation of the brain (such as meningitis or encephalitis)
- Brain tumors

Training

- 4 years of medical school
- 1-3 years of general pediatrics internship/residency
- 3 years of residency training in child neurology, which includes one year of training in adult neurology
- Some complete an additional 1-2 years of training

- Most child neurologists have certification from the American Board of Pediatrics & the American Board of Psychiatry and Neurology.

Red Flags to See Pediatric Neurology

- Seizures or abnormal movements
- Sleep problems
- Developmental Regression
- Weakness/hypotonia
- Vision and/or hearing problems
- Abnormal birth marks
- Family history- especially neurological problems
- Head size/shape- microcephaly or macrocephaly
- Genetic Conditions associated with Neurological Problems

Neurological Exam

- Mental Status
- Cranial Nerves
- Tone & Strength
- Reflexes
- Coordination
- Gait

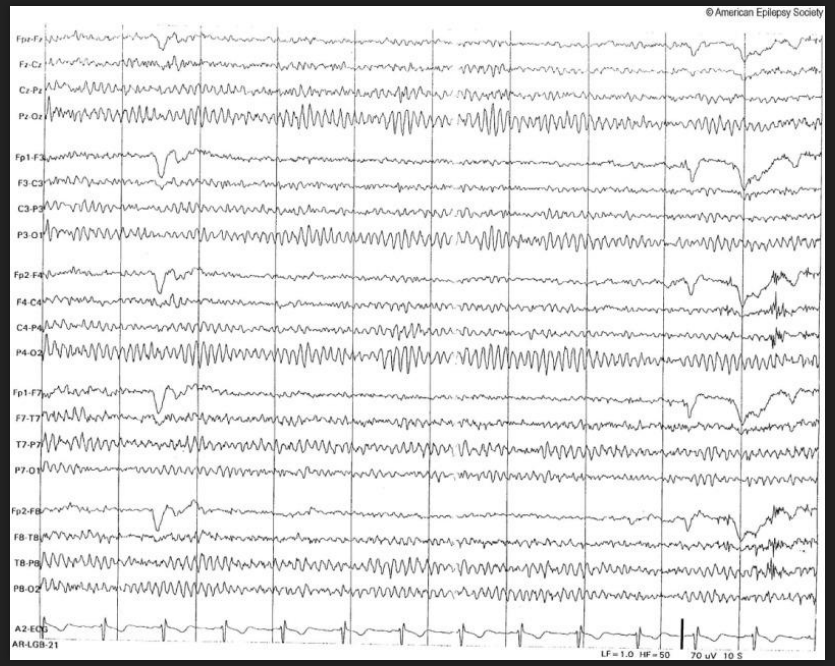
Common Test Ordered

Common Test Ordered

- **EEG (electroencephalogram):** looks for problems with the electrical activity in your brain. This test can be used to look for seizures, and to make sure your child's brain is making the expected types of electrical activity for their age
- **MRI (magnetic resonance imaging):** look for signs of brain tumor, stroke, infection, multiple sclerosis, certain genetic conditions
- **Lumbar puncture (spinal tap):** doctors insert a small needle in the lower back to take a sample of spinal fluid, which surrounds your brain and spinal cord. This can help look for signs of infection or inflammation
- **Blood tests:** may include basic labs checking for electrolyte changes or signs of infection, or more complicated testing such as genetic tests for specific disorders

EEG

- Assess for abnormal seizure activity
- Assess background activity
- May require medication to help with sleep
  - Ex. Clonidine +/- Melatonin



MRI

- Magnetic (NO radiation)
- Looks for brain injury or malformations
- Many times requires sedation
- Takes about 1 hour to complete

Labs

- Metabolic: ammonia, lactic acid, serum amino acids, acylcarnitine profile, urine organic acids
- Muscular: CK level
- Genetic: Fragile X, CMA
  - Consider: Autism/ID panel and/or Whole Exome Sequencing

Autism & Neurological Complications

Epilepsy in Autism

FULL TEXT ARTICLE

The co-occurrence of epilepsy and autism: A systematic review

Sara Lukmanji, Sofiya A. Manji, Sandra Kadhim, Khara M. Sauro, Elaine C. Wirrell, Churl-Su Kwon and Nathalie Jetté

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Highlights

- Autism and epilepsy often co-occur, which has implications for patient management and outcomes.
- This study synthesized data on the incidence and prevalence of autism in epilepsy and vice-versa from 74 studies.
- The median overall period prevalence of epilepsy in people with autism was 12.1% (range: 1.8-60%).
- The median overall period prevalence of autism in people with epilepsy was 9.0% (range: 0.60-41.9%).
- The period prevalence of epilepsy in people with autism, and vice-versa, was higher than estimates in general populations.

Results

Seventy-four studies reporting on 283,549 patients were included. The median overall period prevalence of epilepsy in people with autism was 12.1% while the median overall period prevalence of autism in people with epilepsy was 9.0% when including all population types. When excluding studies that investigated patients with syndromic epilepsy or developmental delay, the median overall period prevalence of epilepsy in people with autism was 11.2% while the median overall period prevalence of autism in people with epilepsy was 8.1%. We observed trends for sex as the prevalence of autism in epilepsy was higher in males while the prevalence of epilepsy in autism was higher in females. It is important to interpret these estimates with caution, as there was significant heterogeneity between studies. Meta-regression found no association between study quality and prevalence or incidence estimates (all p-values > 0.05).

Autism in Epilepsy

Prevalence and risk factors for autism spectrum disorder in epilepsy: a systematic review and meta-analysis

Lauren Strasser ✉, Michelle Downes, Jane Kung, J Helen Cross, Michelle De Haan

Results

A total of 19 studies were found with a pooled ASD prevalence of 6.3% in epilepsy. When divided by type, the risks of ASD for general epilepsy, infantile spasms, focal seizures, and Dravet syndrome were 4.7%, 19.9%, 41.9%, and 47.4% respectively. Studies with populations under 18 years showed a 13.2 times greater risk of ASD than study populations over 18 years, and samples with most (>50%) individuals with intellectual disability showed a greater risk 4.9 times higher than study populations with a minority of individuals with intellectual disability. The main risk factors for ASD reported in the 19 studies included presence of intellectual disability, sex, age, and symptomatic aetiology of epilepsy.

What this paper adds

- Critical evaluation of previous studies examining the prevalence of autism spectrum disorder (ASD) in individuals with epilepsy.
- A meta-analysis of 19 studies showed a pooled ASD prevalence of 6.3% in individuals with epilepsy.
- Studies that included a majority of individuals with intellectual disability or younger population age had a higher prevalence of autism.
- Risk factors reported in studies included presence of intellectual disability, sex, age, and symptomatic epilepsy origin.

Autism & Epilepsy

Conclusion: Patients with autism are at higher risk than the general population for seizures and/or epilepsy

ILAE 2017 Classification of Seizure Types Expanded Version [1]

Focal Onset

Aware | Impaired Awareness

Motor Onset
- automatisms
- atonic [2]
- clonic
- epileptic spasms [2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified [3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms

2 Degree of awareness usually is not specified

3 Due to inadequate information or inability to place in other categories

Autism & Neuroimaging

Review | Open Access | Published: 10 March 2017

Candidate Biomarkers in Children with Autism Spectrum Disorder: A Review of MRI Studies

Dongyun Li, Hans-Otto Karnath & Xiu Xu

Neuroscience Bulletin **33**, 219–237(2017) | Cite this article

Reference	Age range	Brain regions	Methods	Findings in ASD group
Elia *et al.* (2000) [57]	5–17 years	Corpus callosum; midbrain; cerebellar vermis	Area measurements; T-test; regression	No abnormalities in the total vermis, vermis lobules VI-VII, pons, and midbrain
Carper *et al.* (2002) [35]	2–4 years	WM and GM volumes	ROI; SPSS	↑ WMV in frontal and parietal lobes
				↑ GMV in frontal and temporal lobes
Sparks *et al.* (2002) [36]	3–5 years	Cerebrum; cerebellum; amygdala; hippocampus	ROI; SPSS; ANCOVA	↑ TBV and amygdala, cerebellar, and hippocampus volume
Herbert *et al.* (2003) [51]	7–11 years	Cerebrum; cerebellum	ROI; semi-automated segmentation; SPSS; GLM	↑ TBV and total cerebellar volume
Akshoomoff *et al.* (2004) [37]	4–6 years	Cerebrum; cerebellum; cerebellar vermis; TBV	ROI; ANOVA; segmentation	Low-functioning autism: ↑ TBV and cerebral volume; ASD: ↑ TBV, cerebral and cerebellar GMV and WMV, anterior and posterior cerebellar vermis area
McAlonan *et al.* (2005) [56]	10–12 years	GM; WM regional density	VBM; BAMM; SPSS; GLM; MANCOVA	↓ GM density in frontal and parietal areas; ↓ WM density in cerebellum and left internal capsule and fornices
Hazlett *et al.* (2006) [38]	1.5–3 years	Cerebrum; cerebellum	ROI; NLMM; segmentation	↑ GMV and WMV in cerebrum
Hardan *et al.* (2006) [42]	8–13 years	Cortical thickness	SBM; Freesurfer	Total cerebral sulcal and gyral thickness; no significant difference in frontal and occipital areas
Munson *et al.* (2006) [62]	3–4 years	Cerebrum; amygdala; hippocampus	Area measurements; linear modal	↑ Right amygdala volume
Schumann *et al.* (2010) [39]	1.5–5 years	Cerebrum	ROI; SPSS; ANCOVA; segmentation	↑ GMV and WMV in cerebrum; notably in frontal, temporal, and cingulate cortices
Jiao *et al.* (2010) [44]	7–11 years	Cortex	SBM; T-test; Freesurfer	↑ Thickness in left caudal anterior cingulate cortex and left frontal pole; ↓ thickness in right entorhinal, right lateral orbitofrontal, left lateral orbitofrontal, right medial orbitofrontal, left medial orbitofrontal cortex, and right pars triangularis
Hazlett *et al.* (2011) [34]	6–7 months	Cerebrum; cerebellum	ROI; GLM; automatic segmentation; ANOVA	No significant difference in TBV, cerebral cortex, cerebellum, or lateral ventricle volumes
Shen *et al.* (2013) [40]	(Longitudinal) 6–9 months; 13–14 months; 19–21 months	Cerebrum	ROI; LMM; manual segmentation	↑ CSF over frontal lobe at 6–9 mos; ↑ total cerebral volumes at 12–15 mos
Nordahl *et al.* (2012) [63]	2–4 years	Amygdala	ROI; ANCOVA	↑ Amygdala volume at both time points
Dierker *et al.* (2015) [45]	9–12 years	Cortex	SBM; ANOVA; freesurfer	Bilateral differences in sulcal depth in the anterior-insula, frontal-operculum, and temporal-parietal junction
Frazier *et al.* (2009) [64]	7–12 years	Corpus callosum	ROI; area measurement	↓ Volume of corpus callosum
Barnea-Goraly *et al.* (2014) [79]	(Longitudinal) 8–12 years; 10–14 years	Amygdala; hippocampus	Area measurement; rm-ANOVA	No difference in hippocampus of both hemispheres

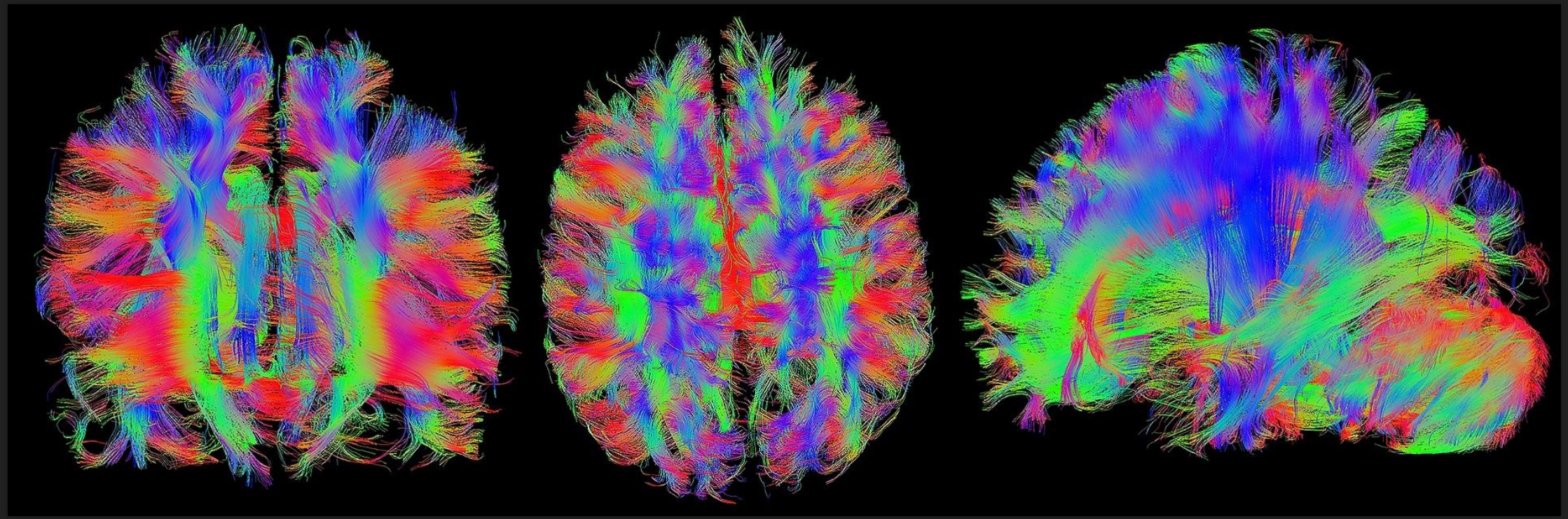
WM, white matter; GM, grey matter; TBV, total brain volume; ROI, region of interest; SBM, surface-based morphometry; VBM, voxel-based morphometry; GLM, general linear models; ANOVA, analysis of variance; ANCOVA, analysis of covariance; rm-ANOVA, repeated measures ANOVA; LMM, linear mixed models; NLMM, non-linear mixed models; SPM, Freesurfer, ad SPSS are data analysis packages.

Neuroimaging Modalities

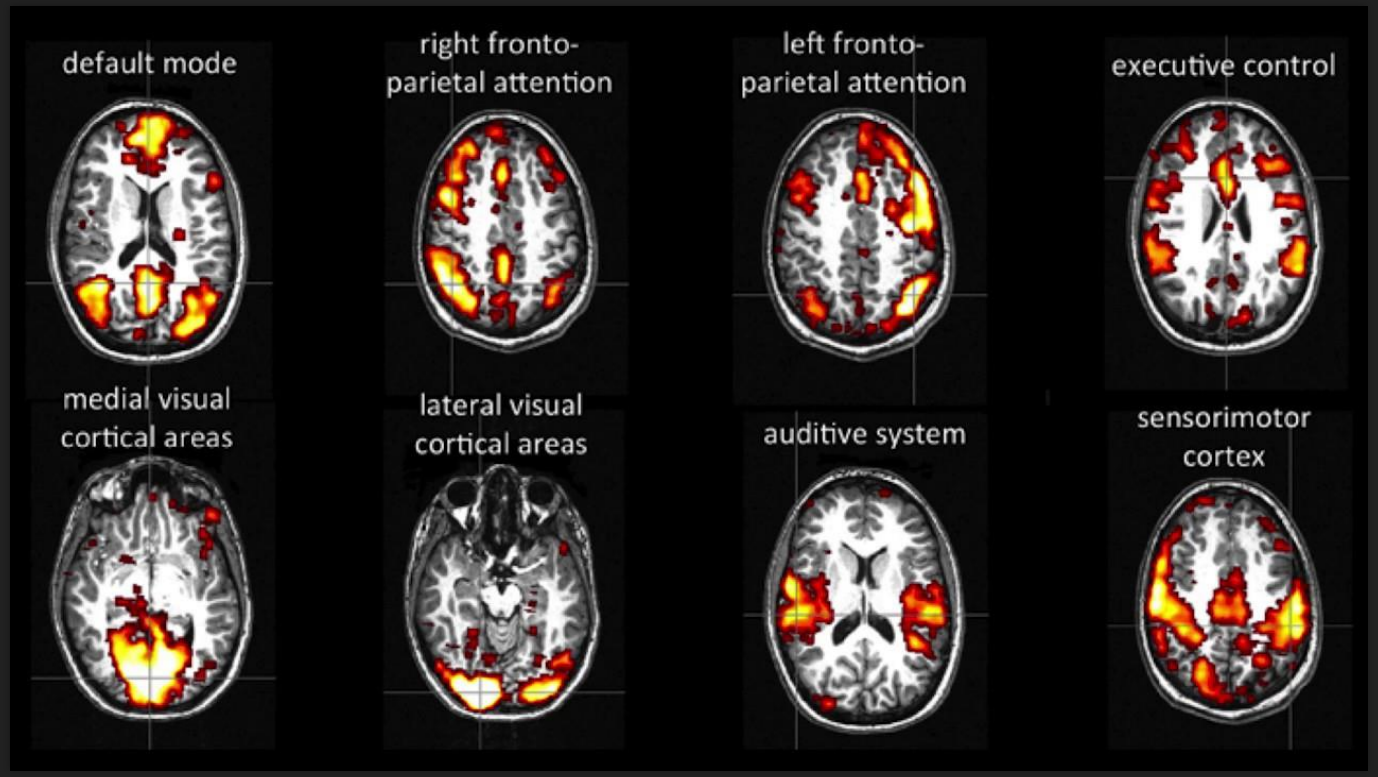
- Diffusion Tensor Imaging (DTI)
  - MRI-based neuroimaging technique which makes it possible to estimate the location, orientation, and anisotropy of the brain's white matter tracts.
- Resting-State Functional MRI
  - Used in brain mapping to evaluate regional interactions that occur in a resting or task-negative state
- MRI Spectroscopy
  - Measures biochemical changes in the brain

Note: these are mostly used on a research basis and not for clinical care

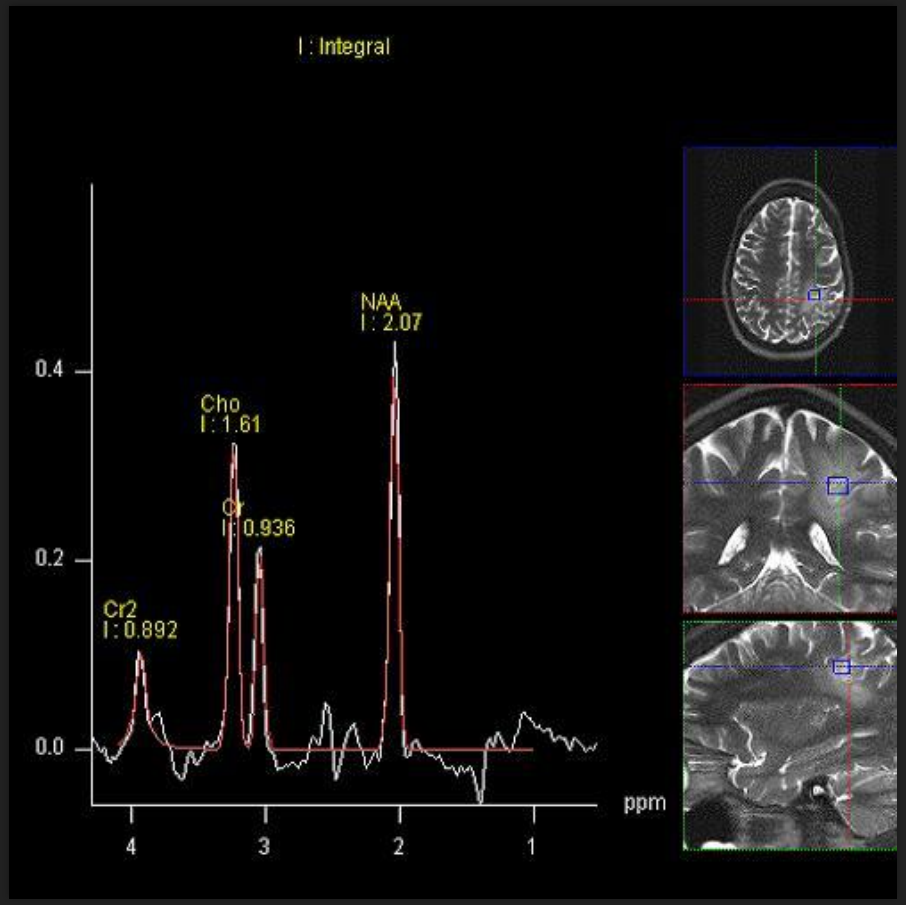
Diffusion Tensor Imaging



Resting State Functional MRI



MR Spectroscopy



MRI approaches	Findings
Structural MRI	*Cortex*
	Increased total GM and WM volumes
	Increased GM and WM volumes in frontal and temporal areas
	Increased cingulate cortex
	Atypical variation of cortical thickness in frontal, temporal, and parietal lobes
	Cerebellum and subcortical areas
	Cerebellum
	Increased total volume
	Increased GM volume
	Decreased WM density
	Amygdala
	Increased volumes in younger children bilaterally
	Trajectory of development of amygdala follows overall trajectory of TBV
	Corpus callosum
	Decreased overall size
	Increased regional volume
	Basal ganglia
	Increased caudate volume
	Atypical shapes of the structures
	Hippocampus
	Increased size of hippocampi in young children
	Enlargement located especially on the right side
	No difference between sides in older children
Diffusion tensor imaging	Decreased FA in the whole brain, frontal lobe, arcuate fasciculus, across the entire CC, and in anterior thalamic radiation
	Increased FA in arcuate fasciculus and in CC in young children
	Increased MD in whole brain, frontal and temporal lobes, and across the entire CC
Resting-state fMRI	Altered functional connectivity in the default mode network
	Hyper-connectivity in striatal-cortical circuitry, precuneus, cingulate cortex, and temporal-frontal circuity
	Under-connectivity in anterior-posterior connections
Magnetic resonance spectroscopy	Decreased NAA levels in general GM and WM, especially in frontal, temporal, cingulate, and caudate areas
	Decreased Cr+PCr levels in general GM and WM, especially in frontal, parietal, temporal, occipital cortex, and thalamus
	Decreased choline levels in cortical areas, temporal lobes, and thalamus
	Increased choline levels in caudate, anterior cingulate cortex, and hippocampus-amygdala complex
	Decreased Glx in GM of frontal, occipital, temporal cortex, and cerebellar regions
	Increased Glx in thalamus and putamen

Autism & Neuroimaging

- **Summary**
  - Increased white and gray matter volume in frontal & temporal lobes
  - Cerebellum most consistent site of abnormality
  - Increased total brain volume
  - Decreased volume of corpus callosum

- **Conclusion:**
  - Many studies are done on small populations
  - Very heterogeneous patient population
  - Most findings are non-specific and clinically insignificant

Neurogenetics & Autism

Neurogenetics & Autism

- >1,000 genes have been reported to be associated with ASD
- 10-20% of patients with ASD have an identifiable genetic condition

Neurogenetics & Autism

- Fragile X Syndrome
- Down Syndrome
- Rett Syndrome
- Tuberous Sclerosis Complex
- Angelman Syndrome
- Phelan McDermid (SHANK3)
- Others….

Fragile X Syndrome

- X-linked dominant
- CGG repeats in FMR1 gene

RESULT(S): NEGATIVE

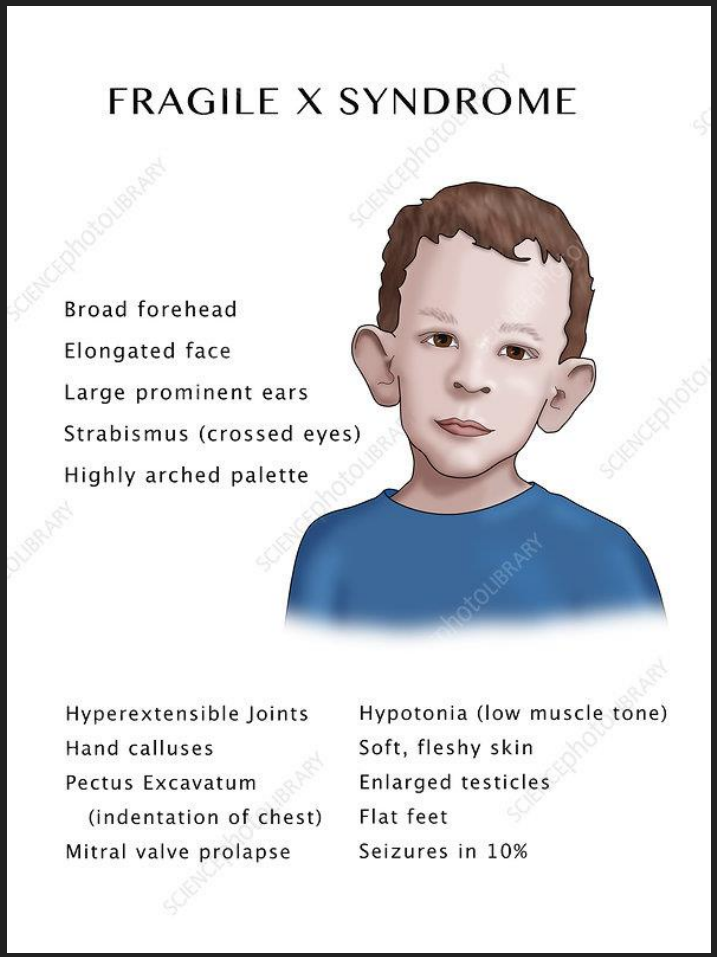
Gene	Mode of Inheritance	Variant	Zygosity	Classification
FMR1	X-Linked	Repeat Number: 30	Hemizygous	Normal

REFERENCE RANGE

Result	CGG Repeat Size
Normal	<45
Intermediate ("grey zone")	45-54
Premutation	55-200
Full mutation	>200

Fragile X Syndrome

- Intellectual Disability
- Autism Spectrum Disorder (15-60%)
- ADHD
- Seizure/Epilepsy (10-20%)



Down Syndrome (Trisomy 21)

- Intellectual Disability (average IQ 50)
- ASD (5-10%)
- Seizure/epilepsy (5-10% children, 50% adults)
- Hypotonia
- Other systemic problems

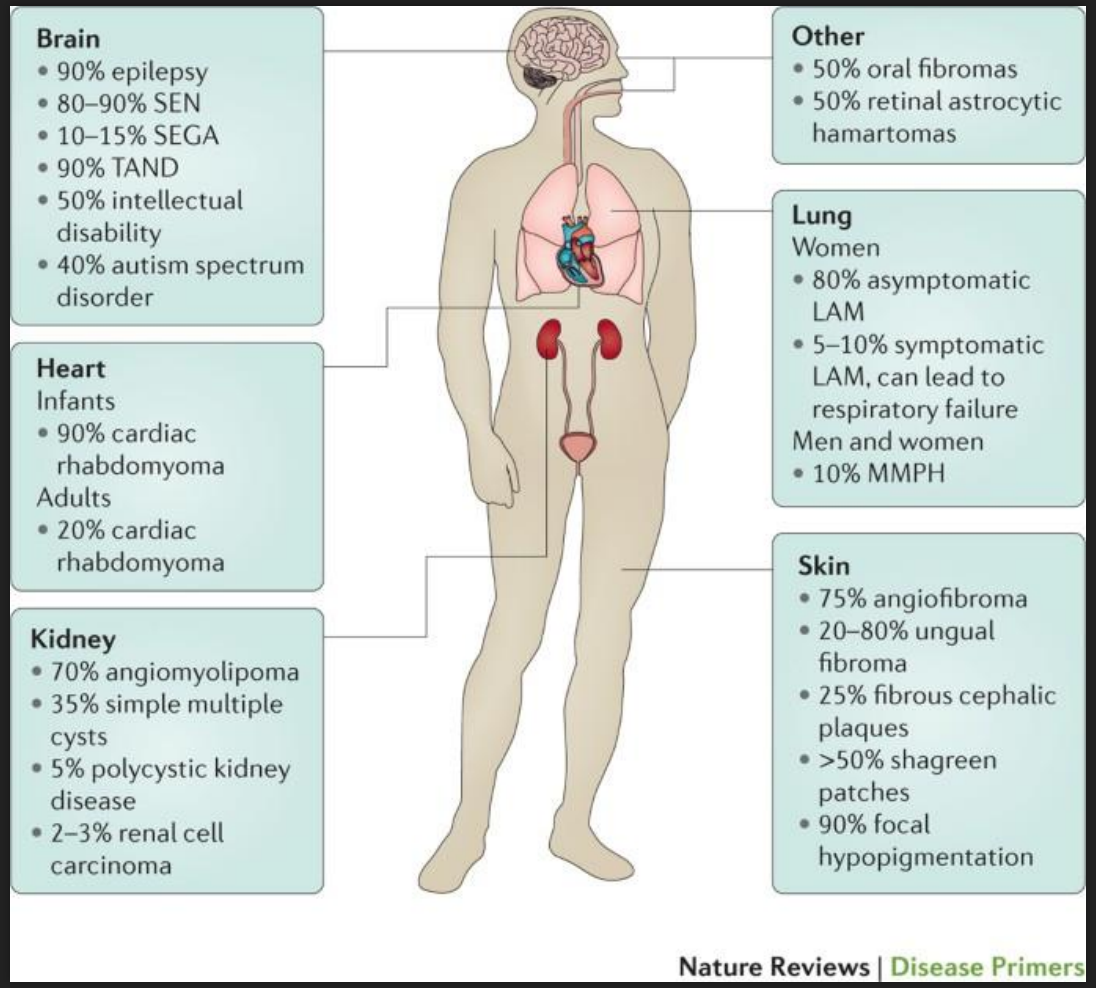
Rett Syndrome

- Mutation in MECP2 on X chromosome
- Mostly in females
  - Males typically lethal in utero
- Developmental regression between 6-36 months of age
- Acquired microcephaly
- Hand ringing
  - https://www.youtube.com/watch?v=53k1EsP5D8k
- ASD
- Seizures/epilepsy (many refractory)
- Gait issues

Tuberous Sclerosis Complex

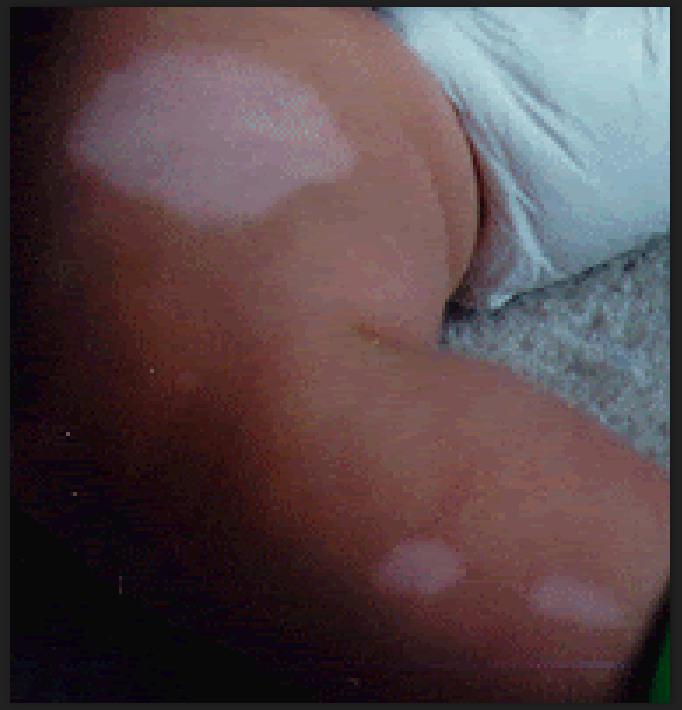
- Genetic mutation in TSC1 or TSC2
  - Autosomal dominant
- Concerns for non-cancerous tumors in brain and other vital organs
  - Many diagnosed in utero due to cardiac rhabdomyomas
- ASD (~50%)
  - More common in TSC2
- Ash leaf spots on skin
- Seizure/epilepsy
  - Infantile spasms could be presenting symptom in infancy
  - https://www.youtube.com/watch?v=VU6qNLOlU_A
- Intelligence ranges from normal to severe ID
  - 40-50% with normal IQ

Tuberous Sclerosis Complex



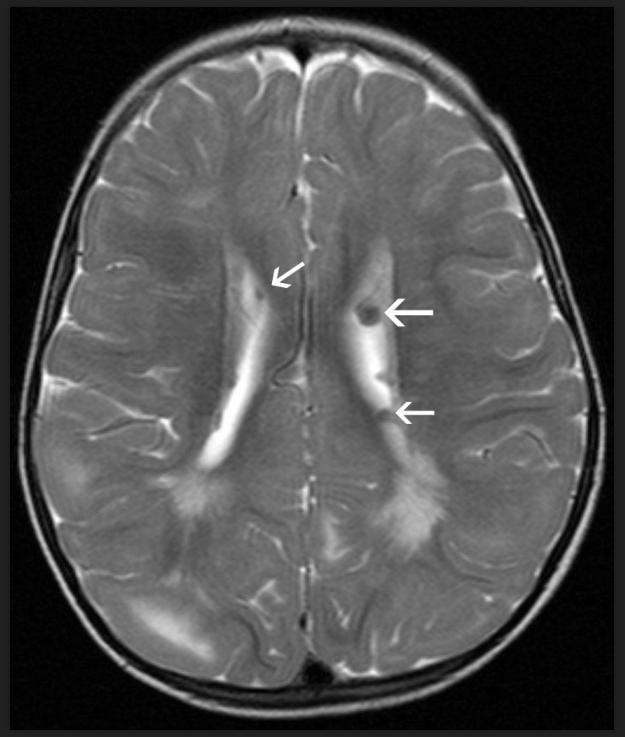
Tuberous Sclerosis Complex

Ash Leaf Spots



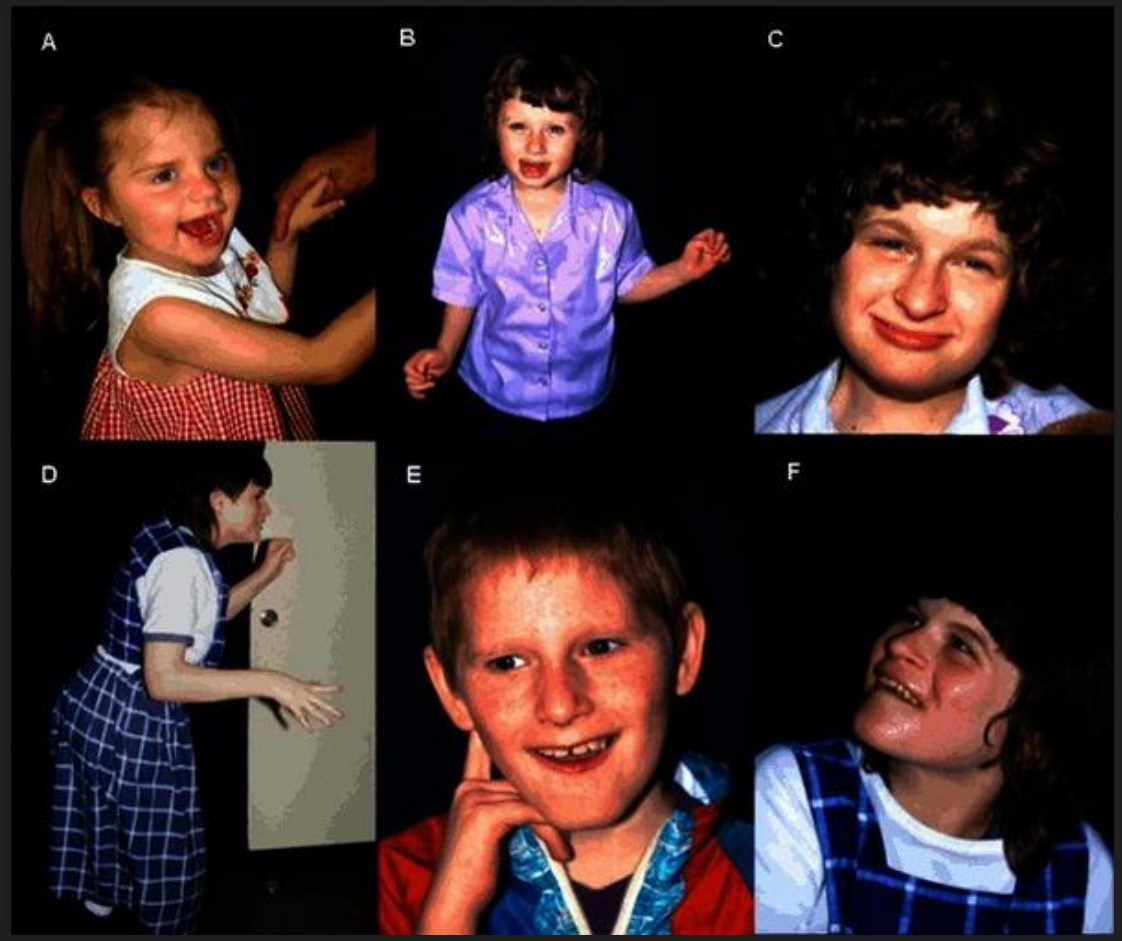
Cortical Tubers &

Subependymal Nodules



Angelman Syndrome

- "Happy Puppet Syndrome"
- Deletion/mutation in UBE3A gene on chromosome 15
- Microcephaly
- Global developmental delay/ID
- ASD in 20-30%
- Seizures/epilepsy (75%)
  - Myoclonic seizures



Landau-Kleffner Syndrome

- Begins 2-8 years of age (average 5-7 years of age)
- Rare form of epilepsy that typically occurs during sleep
  - Electrical Status Epilepticus in Sleep (ESES) common
- Many diagnosed with ASD due to language regression
- Cause is unknown although mutation in GRIN2A found in small percentage of patients
- Reason why most neurologists will order an EEG in patients with ASD, especially those with history of developmental/language regression
- Neuroimaging normal
- Non-syndromic in appearance

Phelan-McDermid Syndrome

- Mutation in SHANK3 gene due to deletion in 22q13
- ASD rates unknown but likely up to 75-90%
- Epilepsy in up to 40-50%
- Global developmental delay/Intellectual Disability

Other Neurological Causes

Birth-related Events Increasing Risk of ASD

- Low birth weight
- Extreme prematurity (before 26 weeks)
- Intrauterine infection during the pregnancy
- Male
- In utero drug exposure
- Injuries to cerebellum

Other Causes

Most “causes” for autism are unknown

Studies show that with neurological and genetic work-up that only 20-30% patients will receive a clinical diagnosis

More clinical studies and research is needed

Questions