

Autism Spectrum disorders: developmental disconnection syndromes

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Definition

- clinical assessment
- onset of 3 disturbances < age 3
 - social
 - verbal & nonverbal communication
 - restricted interests & repetitive behavior

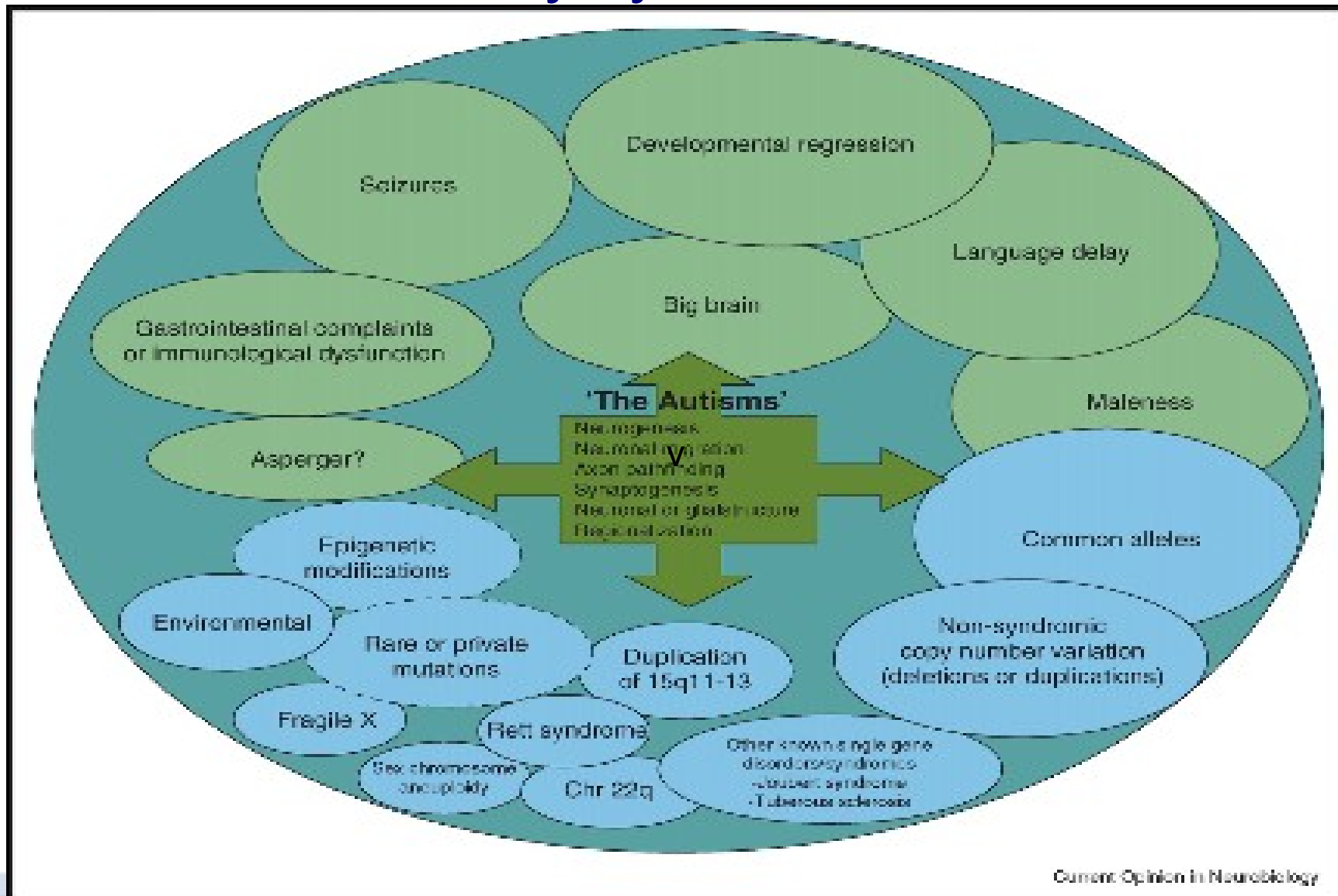
However, sig. differences in extent & quality of symptoms

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- language delay observed in only $\frac{1}{2}$ of subjs
- <50% have sig. cognitive impairment
- soc. impairment expressed differently: aloof vs. active but odd interaction
- diffs in developmental timecourse: onset in infancy to 2-3 years
- varied treatment responsiveness

Thus, ASDs heterogeneous

- may be better to think of ASDs as 'the autisms' rather than unitary syndrome:



Hypothesis: ASDs form 'developmental disconnection syndrome'

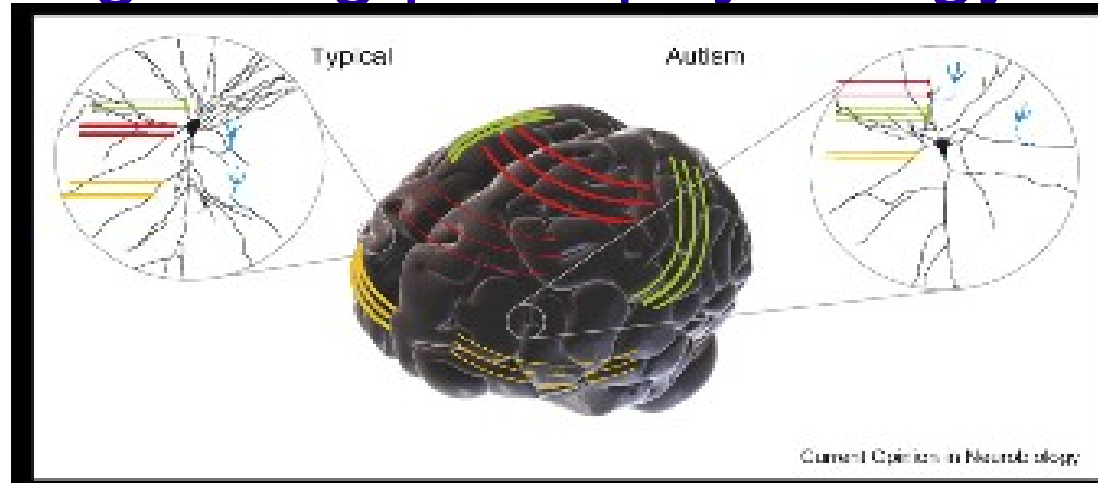
- disconnection in ASDs may be a failure in the normal development of connectivity between
 - higher association areas
 - multimodal cortical regions
- ...may include weakening of already formed connections &/or failure of certain connections to est. correct initial organization
 - prenatal: neuronal migration, axon pathfinding
 - postnatal: dendrites, synaptogenesis, pruning
- subtle timing disturbances affect connectivity

- neuronal processes of growth & organization occur across extended period prenatally and postnatally → interaction of genes & environment
- diffs in timing of these processes →
 - specific disruptions depends on timing of insult

Heritability

- twin & family studies suggest autisms among most heritable neuropsychiatric disorders
 - 25 to 100x greater risk of autism in a sibling born to a family w/ an autistic child
 - severity of the 3 core disturbances & associated features show familial clustering
 - twin studies: the 3 core traits highly heritable
- genetic risk factors may converge on modulation of interrelated neurodev. events that broadly affect physical & funct. connectivity of higher-order association areas i.e. cerebral cortex

(Limited) clues regarding pathophysiology of autisms



- altered packing density of cells
- minor & variable disruption of dendritic orientation
- reduced size & spacing of radial minicolumns of neurons in diff. areas e.g., frontal lobe
- selective reduction in cell number in some forebrain structs
- microscopic abnormalities throughout cortex → suggests distributed atypical development

Macrocephaly trend in autisms

- consistent with concept of more widespread circuitry disturbances; observed in ~20% of children w/ ASDs
 - both white & grey matter abnormally lg. throughout cortex e.g., frontal, temporal, parietal lobes
 - size of white matter tracts, neuron #s & densities, dendritic arborization in grey matter all contribute to brain size & regulated over extended pre- and postnatal period
- cog. skills more sig. correlated w/ dev. trajectory of brain volumes over time than w/ static brain volume

Autisms not synonymous with global intellectual disability

- key disconnection must be between several frontal lobe & temporal lobe multimodal higher-order association cortices
 - e.g., frontolimbic, frontoparietal, interhemispheric connections
- this model would include disruption of initial architecture of connectivity, & this influences exp-dependent processes crucial for continued dev. & reorganization of connections
 - disconnection of dorsolateral prefrontal & anterior cingulate cortex are necessary to develop joint attention in early infancy

Intersection of autisms w/ development of functional connectivity

- Timing, location, and degree to which gene expression is disrupted dictate emergent phenotype
- circuit formation process is hierarchical & depends on interaction between genetic networks and experience
 - social behavior & verbal/nonverbal communication depend on capacity of earlier developing sensory & motor components
- connectivity of association areas exhibits longer maturation, thus more vulnerable

Linking neurodev. etiology & genetics w/ autisms

- challenging because
 - moderate-to-weak genetic associations
 - likely involvement of multiple genes
 - difficulties of replication in heterogeneous clinical populations
- genetics of autisms complex, multigenic interactions & multiple rare genetic mutations
- any specific risk element likely related to specific impairments in aspects of cogn. & behavior e.g., social behavior, language, & repetitive behaviors, *rather than* traditional clinical diagnosis

However, progress despite these challenges...

- Examples include:
 - families with multiple persons with ASDs revealed mutations that disrupt genes encoding Neuroligin 3 & 4, which interact w/ proteins called β -Neurexins during synaptogenesis & influence copy number and copy variation, contributing to ASD risk
 - Amish CNTNAP2 gene mutation → rare neuronal migration disorder: seizures, language delay, intellectual disability & ~2/3 have ASDs
- Suggests huge overlap between autisms & more general disruption of brain development

Many factors at play in ASD dev.

- specific quantity & topology of neuronal migration deficits or suboptimal function of synapses on malformed dendrites may mean mental retardation, severe autism, or milder ASD e.g. Asperger's, or any other
 - i.e. which systems functionally disconnected and how severe and widespread disconnect is will contrib. to phenotype

Risk alleles of autism candidate genes that influence connectivity

- Hepatocyte growth factor (HGF) receptor *MET* associated with ASDs
 - MET signalling affects neocortical & cerebellar neuronal growth & maturation, particularly interneuron development & pyramidal cell dendritic growth
 - mice studies suggest low MET expression result in seizures, anxiety, atypical social behavior
 - strong association of common 'C' allele in promoter region of *MET* gene in families w/ multiple persons w/ASDs. 'C' allele causes 2X decrease in *MET* promoter activity

Conclusions

- autism disorders involve disturbances to complex information processing abilities at multiple levels of dev. → heterogeneous
- circuit dev. hierarchical, progresses from first-order pathways to complex higher-order connections
- cellular basis for dysfunctional circuits poorly understood in autisms compared w/ syndromic neurogenetic disorders
- circuitry needs to be better understood & animal models interpreted w/ diff. evolutionary contexts in order to consider human specialization e.g. JA, language



Thanks!