Research in Brain Development and Implications for Speech, Language, and Hearing

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Speech, Language,
Hearing Sciences

Disclosures

Financial

- Receiving an honorarium for this presentation
- No other financial implications

Non-Financial

- **ASHA Board of Directors, Vice-President for Finance** (unpaid volunteer)
- **Professor Emeritus**, Auburn University Department of Speech, Language, and Hearing Sciences
- 40 years as University Professor at UU, FAU, UGA, AU
- **Specialties:** Neuroscience, Neuroanatomy/Neurophysiology, Neurogenic Speech & Language Disorders, Neuroaudiology, AAC

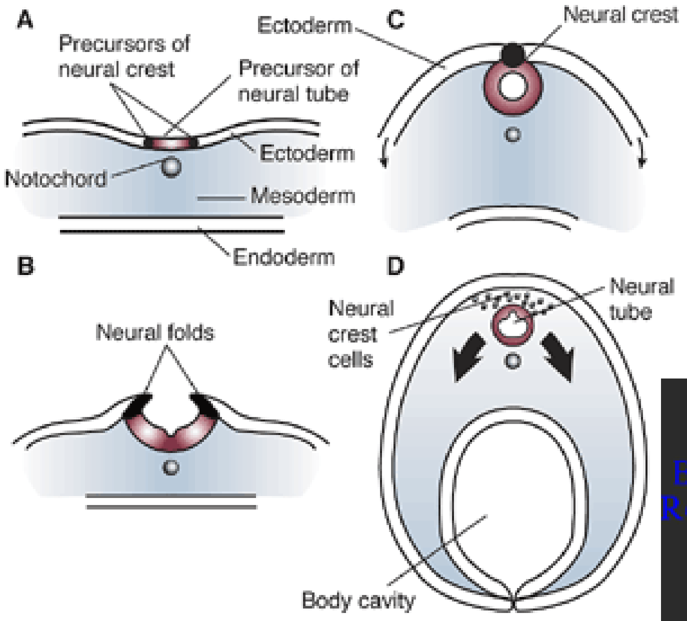
Overview of Presentation

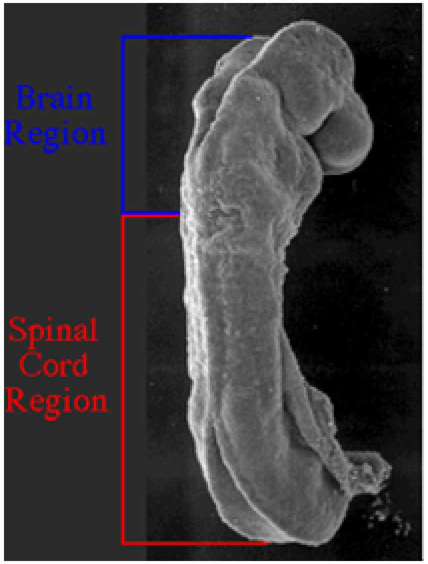
- A little background on prenatal and post natal brain development
- A little background on genetic analysis techniques
- Specific types of speech, language, and hearing disorders linked to abnormal brain development
  - FOXP2 gene – the original “speech & language gene”
  - Autism spectrum disorders
  - Developmental apraxia of speech/devel. verbal dyspraxia
  - Stuttering
  - Auditory Disorders
- Implications for speech-language pathology and audiology

Research in Brain Development:

NORMAL PATTERNS OF BRAIN DEVELOPMENT

Brain Development: Embryonic

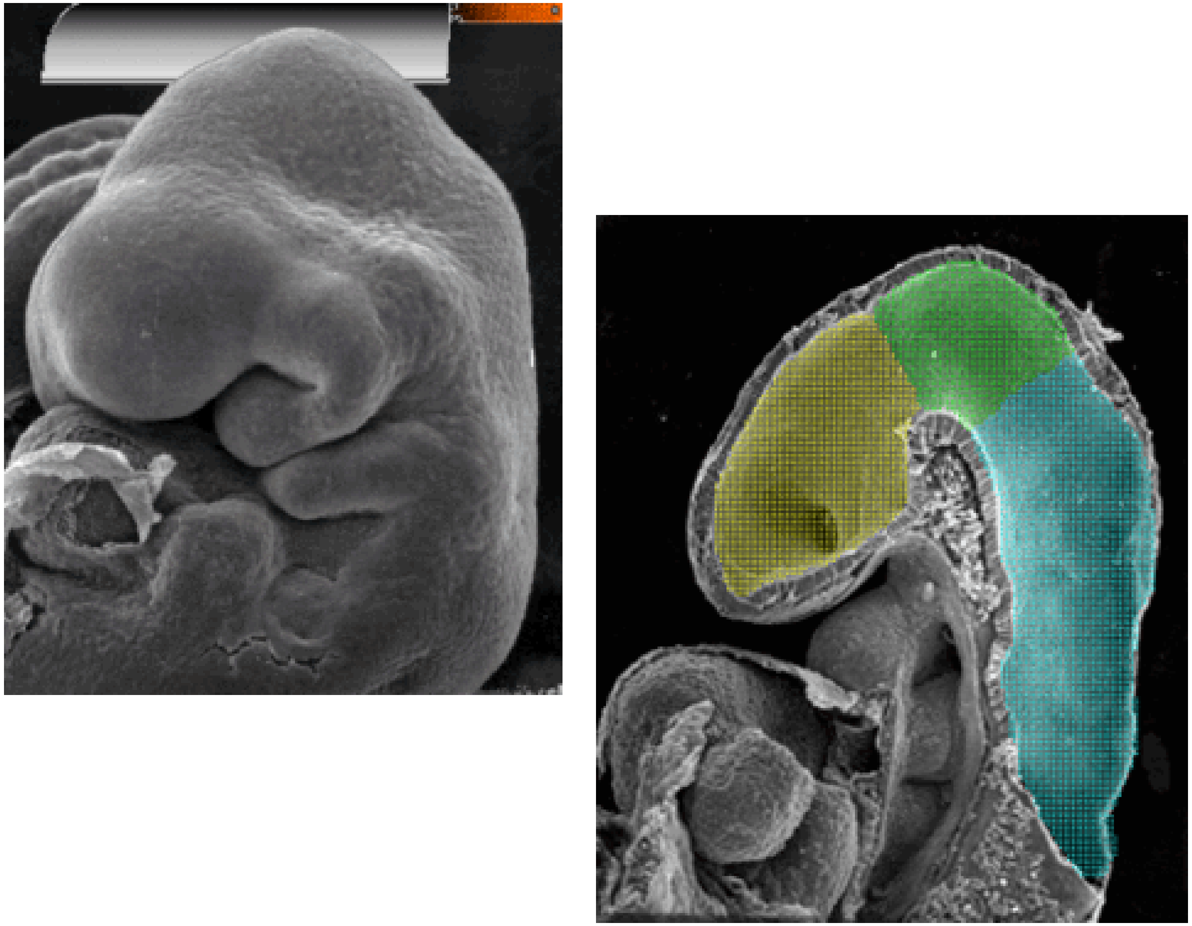




- Early in embryo development, a strip of specialized cells called the notochord (A) induces cells of the ectoderm directly above it to become the primitive nervous system (i.e., neuroepithelium).
- The neuroepithelium then wrinkles and folds over (B). As the tips of the folds fuse together, a hollow tube (i.e., the neural tube) forms (C)—the precursor of the brain and spinal cord.
- Cells originating from the fused tips of the neuroectoderm (i.e., neural crest cells) migrate to various locations throughout the embryo, where they will initiate the development of diverse body structures (D).

(from Goodlett & Horn, 2001)

Brain Development: Embryonic



A cut through the recently closed cranial neural tube illustrates

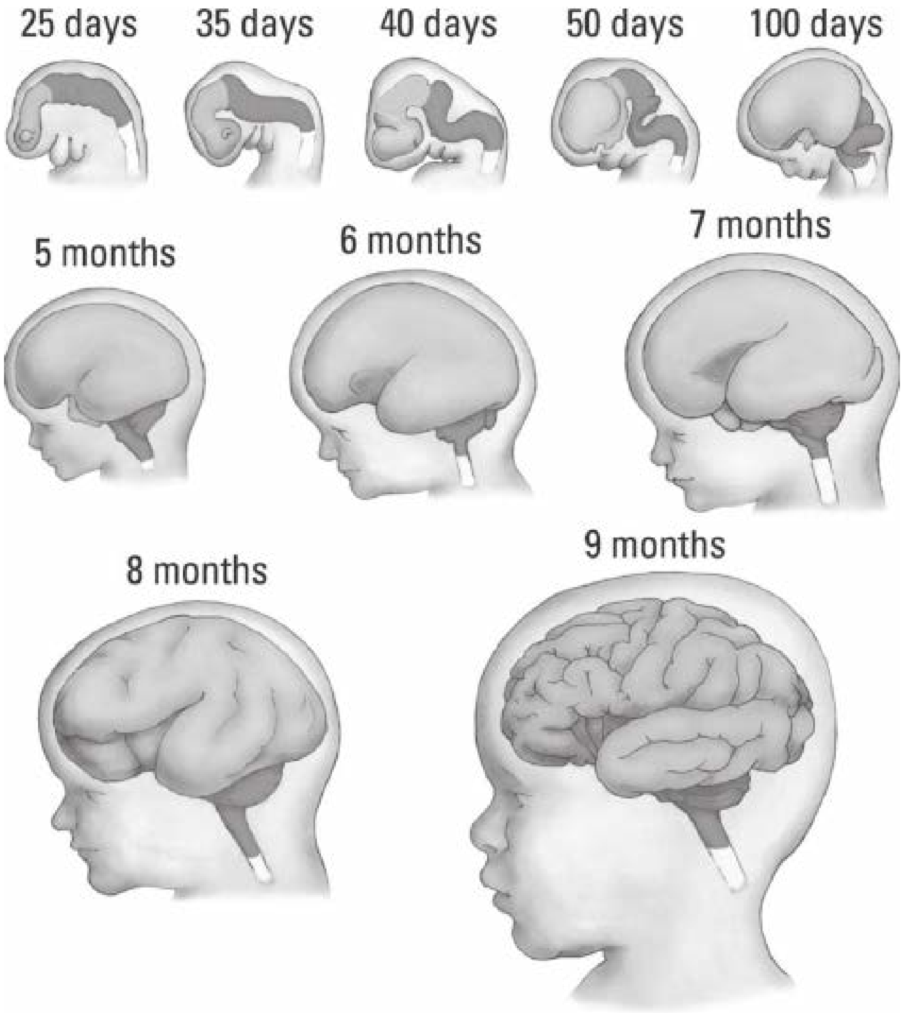
- **forebrain** (prosencephalon),
- **midbrain** (mesencephalon),
- **hindbrain** (rhombencephalon).
- Images are mouse embryo at 10 days/5weeks in human: *(http://www.med.unc.edu/embryo_images/unit-nervous/nerv_htms/nervtoc.htm)*

Brain Development: Gestational

- The development of the human brain is a dynamic process that continues throughout gestation.
- Early gestational period: basic CNS structural development and neural proliferation and dissemination occur.
- Later stages center on cortioconeurogenesis - process of neural development and connectivity between various cortical layers of the brain
- Subcortical neurons are detectable as early as 10 weeks gestation, however neuronal proliferation continues through mid-gestation and the maturation process continues to the end of gestation.
- There is a linear increase in brain volume with increasing gestational age in cerebral and cerebellar tissues.
- During the last 5 weeks of gestation there is a significant increase in dendritic connections and sulci formation.

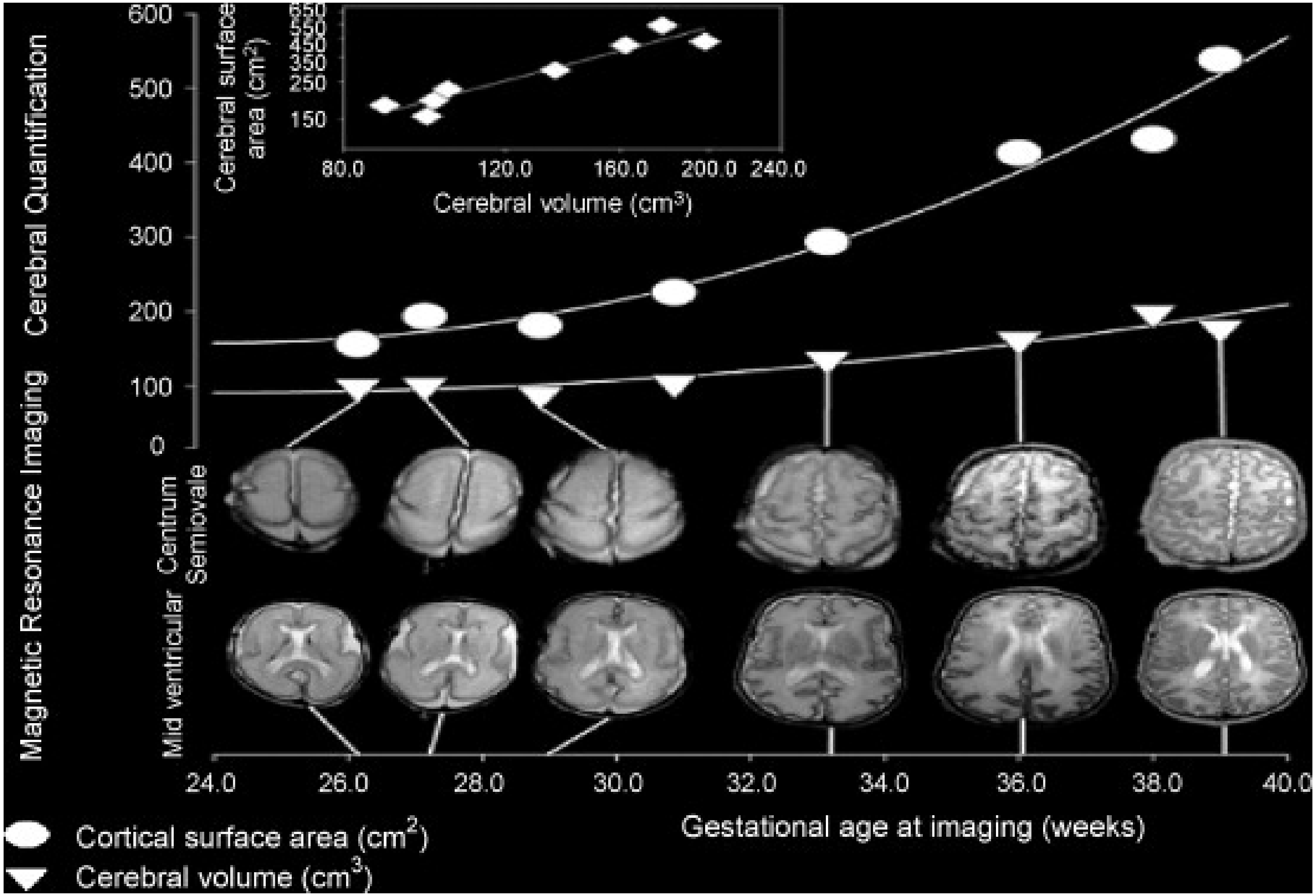
(Leviton and Gressens, 2007; Adams-Chapman, 2006; Kinney, 2006)

Brain Development: Gestational



Changes in brain volume and maturation with increasing gestational age. (from Kapellou et al; 2006).

Brain Development: Gestational



Changes in brain volume and maturation with increasing gestational age.

Top Row MRI Images: Superior View

Lower Images: Mid-Brain Interior

(from Kapellou et al; 2006)

Brain development: Birth – 2 years

- Structurally examined the brains of 98 children: 84 children at 2–4 weeks of age, 35 at 1 year and 26 at 2 years of age using Siemans head-only 3T MRI scanner
- **Total brain volume increased 101% in the first year**, with a **15%** increase in the second.
- Majority of hemispheric growth was by **gray matter, which increased 149% in the first year**; hemispheric **white matter volume increased by only 11%**.
- **Cerebellum volume increased 240%** in the first year.
- **Lateral ventricle volume increased 280% in the first year**, with a small decrease in the second.
- **Caudate N. increased 19%**, **Hippocampus 13%** from age 1 to 2.

Knickmeyer, Gouttard, Kang, et. al. (2008)

Brain development: Birth – 2 years

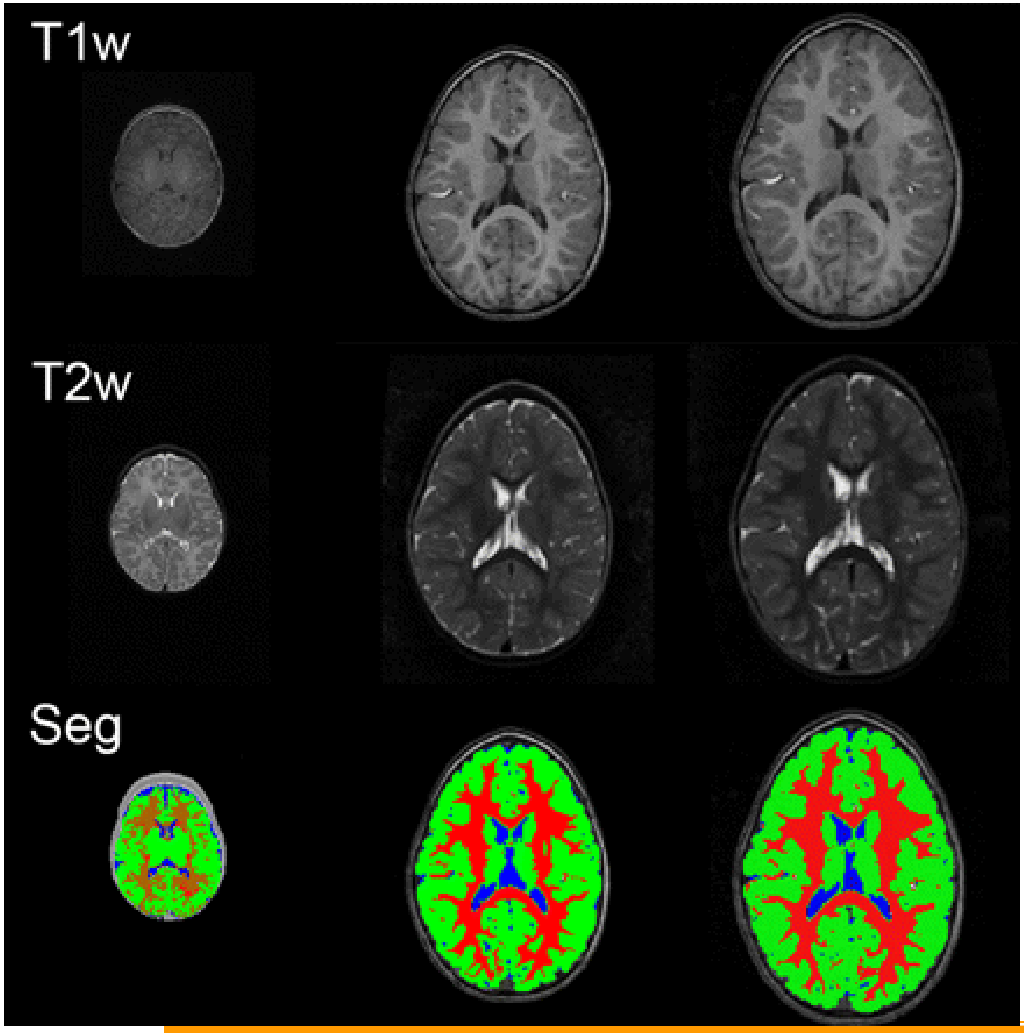
Summary

- There was robust growth of the human brain in the first two years of life, driven mainly by gray matter growth.
- In contrast, white matter growth was much slower.
- Cerebellum volume also increased substantially in the first year of life.

These results suggest the structural underpinnings of cognitive and motor development take place in very early childhood, as well as the **potential pathogenesis of neurodevelopmental disorders**.

(Knickmeyer, Gouttard, Kang, et. al. (2008)

Brain Development: Birth - 2 years



Example of axial slices from a single subject at birth (column1) 1 year (middle column), and 2 years (right column).

In the lower set, colors represent different brain components: cerebrospinal fluid (blue), gray matter (green), myelinated white matter (red), unmyelinated white matter (brown).

(From Knickmeyer, Gouttard, Kang, et. Al., 2008)

Brain Development: Birth - 2 years

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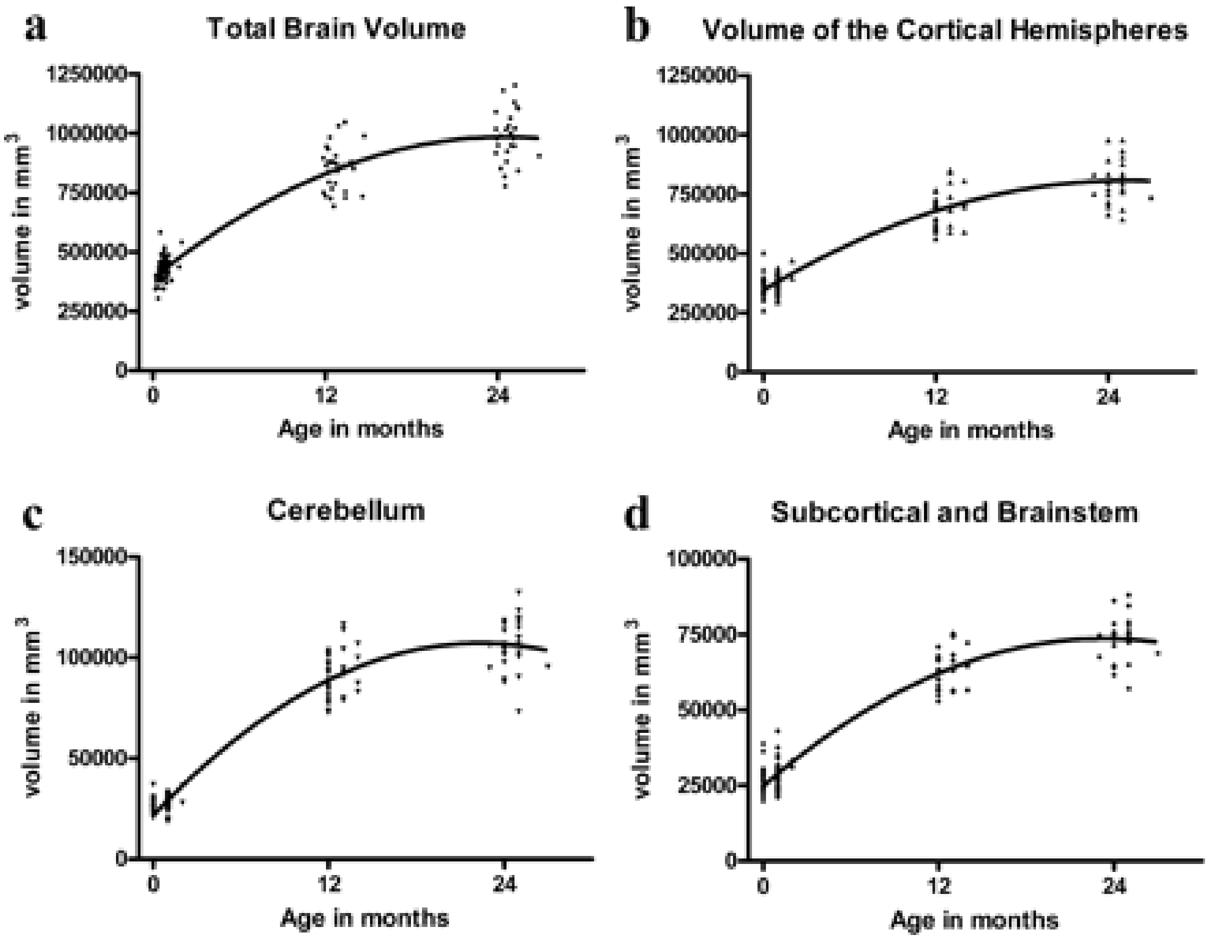

Homogenity of growth patterns: Scatterplots showing brain growth in the first 2 years of life.

(a) Total volume

(b) Cortical Hemispheres

(c) Cerebellum vol.

(d) Subcortical & Brainstem volume

(From Knickmeyer, Gouttard, Kang, et. al., 2008)

Rapid and Dynamic Brain Development: Implications

The act of Communication: (1) auditory and visual reception of communication signals, through (2) processing, (3) reasoning, (4) response formulation (on multiple levels) and (5) provision of verbal, gestural/expressive, or written communication, is clearly a "whole brain" act.

The rapid and dynamic nature of brain development from conception through 2 years of age implies that communication is extremely susceptible to a number of threats, both prenatally and postnatally:

- Genetic disorders
- Metabolic disorders
- Disease
- Injury and insult

Research in Brain Development:

IDENTIFYING GENES FOR COMMUNICATION DISORDERS

Identifying Communication Disorder Genes

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I am shortly going to talk about specific genes linked to specific communication disorders. Determining if a particular speech, language, or hearing disorder has a genetic basis involves a multistep process of increasingly narrow scope:

1. **Heritability studies**
2. **Karyotype analysis**
3. **Genetic linkage analysis**
4. **Genetic association studies (positional cloning)**
5. **Genome-wide associational studies.**

(adapted from Gibson & Gruen, 2008, Uffelmann, Huang, Munung et al 2021)

Identifying Communication Disorder Genes

Heritability studies

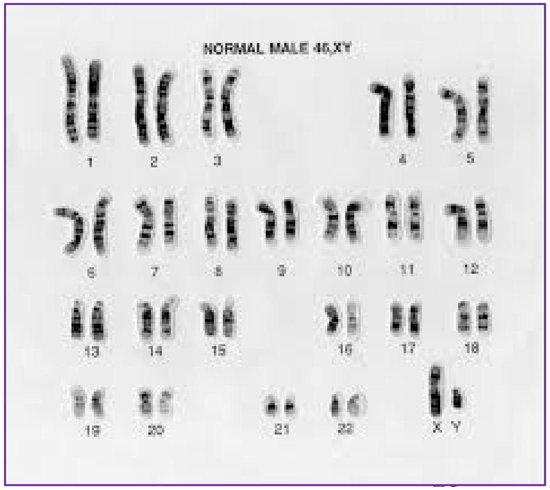
- While a specific trait or disorder may run in a family, that is not enough to establish that it is genetic (familial nature may instead be due to shared environment or other epigenetic factors).
- Most common method used to confirm that a trait is at least partly heritable is a **twin study**
- Examines **concordance of the trait in monozygotic/maternal twins, (genetically identical)**, compared to concordance in **dizygotic/fraternal twins (not genetically identical)**.
- **Significantly higher concordance in monozygotic twins implies that the trait has a genetic component**.
- **Statistical analysis can estimate the degree of variation in a trait due solely to genetics**; this is known as the trait's ***heritability***.

Identifying Communication Disorder Genes

Speech, Language, Hearing Sciences

Karyotype analysis

- Microscopic analysis of peripheral white blood cell chromosomes
- Stained (with giemsa) to distinguish characteristic banding patterns for each chromosome.
- Detects chromosomal deletions or duplications, as well as the exchange of large chromosomal segments, called translocations (example – trisomy 21/Down Syndrome
- FOXP2 first identified with karotype analysis
- Karotype analysis incapable of examing DNA sequences



Identifying Communication Disorder Genes

Genetic Linkage analysis

- Determines the chromosomal regions that contribute to the development of the trait/disorder, by **comparing genotypes from multiple members across several generations of families** affected by the trait in question.
- Uses **“markers” (fragment of DNA sequence at a unique location within the entire genome that varies with a known frequency within a population)** Single Nucleotide Polymorphisms (SNPs, pronounced “snips”)
- The **variation of single SNPs has been determined by compiling the results of many sequencing studies in open-source databases**. Geneticists call **each unique variant of a marker an “allele”.**
- By tracing the lineage of marker alleles across generations and comparing it with the lineage of the trait/disorder in the family, researchers can **identify markers within a specific chromosomal region that are inherited in the same pattern as the trait/disorder (specific susceptibility locus)**.

Identifying Communication Disorder Genes

Genetic Association studies (positional cloning)

- **Narrow scope/in-depth look at specific susceptibility loci identified in genetic linkage studies**
- **Compare the frequency of marker alleles in affected subjects (cases) to the frequency in matched unaffected controls.** The premise of these studies is that, due to historical recombination events over many generations, **marker alleles found significantly more often in affected individuals must be in close physical proximity to the disease-causing mutation.**
- **Requires large numbers of affected individuals, along with large numbers of control participants.**

Identifying Communication Disorder Genes

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Genome-Wide Associational Studies (GWAS)

- **With completion of the human genome project, the rules changed dramatically.**
- **Has provided gene-chip technology, in which one million markers spanning the genome can be tested for association with a trait or disease.**
- Major drawback to GWAS is the huge number of markers needed to cover the genome, which greatly increases the likelihood of false-positive associations due to multiple testing.
- Best dealt with using several thousand cases and at least as many controls, making GWAS expensive and complicated, and effectively impossible for low incidence disorders

(Zondervan & Carvon, 2007; Uffelmann, Huang, Munung, et al, 2021)

Research in Brain Development:

FOXP2 – THE CURIOUS CASE OF THE “SPEECH & LANGUAGE GENE”

FOXP2 – the Curious Case of the Speech & Language Gene

Conventional wisdom long held that virtually all cases of familial speech and language impairments have multifactorial, polygenic transmission patterns

- 1990 Hurst, Baraitser, Auger, Graham, and Norell, published the results of their investigation into **3 generations of a British family (identified as KE family)** with an unusually high prevalence (50%) of **oral motor and developmental verbal dyspraxia (Childhood Apraxia of Speech)**
- What was remarkable was that the transmission pattern reflected a **Mendelian (monogenic) autosomal dominant transmission pattern, a mutation of a single gene on an autosome (non-sex chromosome)**

FOXP2 – the Curious Case of the Speech & Language Gene

- In 1998, Fisher, Vargha-Khadem, Watkins, Monaco, and Pembrey conducted **a genome-wide scan** (via a karotype study, as described earlier) **of affected and unaffected KE family members**, and reported **affected members all carried a mutation in a gene on chromosome 7.**
- **The Human Genome Nomenclature committee named the location on chromosome 7 “*SPCH1*” (speech and language disorder -1)**
- Further investigation by several of the team members (Lai, et al, 2000; Fisher, et al, 2001) **indicated a specific mutation in a gene located at 7q31 on chromosome 7**

FOXP2 – the Curious Case of the Speech & Language Gene

- **Lai, et al, 2000 also identified an individual who was unrelated to the KE family, but had a similar type of speech and language disorder.**
- In this case the child, known as CS, carried a chromosomal rearrangement (a translocation) in which part of chromosome 7 had become exchanged with part of chromosome 5. The site of breakage of chromosome 7 was located within the SPCH1 region .
- Work by Fisher, et al (2001) indicated that all affected individuals, both KE family members and CS, carried a mutation in **a specific protein-coding gene**. The gene coded a novel member of **the forkhead-box (FOX) group of transcription factors involved in gene regulation**, and was **given the name FOXP2**. The mutation results in an amino-acid substitution at a crucial point of the DNA-binding domain of the FOXP2 protein, disrupting its function.

FOXP2 – the Curious Case of the Speech & Language Gene

- **FOXP2 orthologs have been identified in all mammals for which complete genome sequencing has taken place, as well as in other species, such as songbirds.**
- **Genetically altered mice with a single copy of FOXP2 have significantly reduced vocalizations as "pups"** (Shu, Lu, Zhang, et al, 2005)
- **Examination of FOXP2 in zebra finches indicates upregulation of activity in young finches leaning song patterns**
- **Knockdown of the gene's regulation of basal gangliar areas in young finches results in incomplete and inaccurate song imitation** (Haesler, Rochefort, Georgi, et al, 2007)

FOXP2 – the Curious Case of the Speech & Language Gene

Speech, Language,
Hearing Sciences

- Aside from a polyglutamine tract, human FOXP2 differs from chimp FOXP2 by only two amino acids, mouse FOXP2 by only 3 amino acids, and zebra finch FOXP2 by only 7 amino acids.
- **A recent extraction of DNA from Neanderthal bones indicates that Neanderthals had the same version (allele) of the FOXP2 gene as modern humans** (Krause, Lalueza-Fox, Orlando, et al, 2007).
- **FOXP2 is a transcription factor that controls the expression of other genes. It is not the sole factor in language but plays a crucial role in the development of the neural pathways necessary for speech.**

FOXP2 – the Curious Case of the Speech & Language Gene

- Lai, Gerelli, Monaco, Fisher, and Copp (2003) reported **FOXP2 expression in several brain structures including the cortical plate, basal ganglia, thalamus, inferior olives and cerebellum**. The authors saw the data as supporting a role for *FOXP2* **in the development of corticostriatal and olivocerebellar circuits involved in motor control.**
- Lai et al reported concordance between regions of early expression and later sites of pathology suggested by neuroimaging. **They felt the homologous pattern of *FOXP2/Foxp2* expression in human and mouse argues for a role for this gene in development of motor-related circuits throughout mammalian species.**

FOXP2 – the Curious Case of the Speech & Language Gene

- The Lai et al study provides support for the hypothesis that **impairments in sequencing of movement and procedural learning might be central to Childhood Apraxia of Speech**, the original *FOXP2*-related speech and language disorder.
- One might ask how a FOXP2 mutation might be detected other than via genetic analysis. The effects of FOXP2 disorders can be seen via neuroimaging techniques. Vargha-Khadem, Gadian, Copp, and Mishkin (2005) utilized **fMRI analysis of individuals with CAS performing silent verb generation and spoken word repetition tasks. fMRI demonstrated underactivation of Broca's area and the putamen (a basal ganglia area involved in motor control).**

FOXP2 – the Curious Case of the Speech & Language Gene

- It appears, however, that DVD is not the only disorder linked to FOXP2 mutations. The Oxford team knew that *FOXP2* turned other genes on and off in the brain, so mutations in FOXP2 *would have effects on multiple neural pathways downstream of the gene, resulting in a variety of speech and language disorders.*
- They investigated human neurons grown in the lab to see which parts of the genome were bound by *FOXP2* protein. They quickly discovered that *FOXP2* had a strong attraction for sections of DNA that controlled a gene called *CNTNAP2*, which codes for a protein that affects how neurons interact with each other during development. They discovered some FOXP2 mutations down-regulate *CNTNAP2* .

FOXP2 – the Curious Case of the Speech & Language Gene

- Next, the researchers sifted through a database of DNA from 847 people in 184 families that have SLI. A particular CNTNAP2 alteration (single nucleotide polymorphism, rs17236239) was significantly associated with *Specific Language Impairment*, which affects up to 7% of children. It was the first time were able to identify a particular gene that's involved in common forms of language impairment.
- Adding further support to the intersection of *CNTNAP2* and language, Fisher's collaborators at the University of California, Los Angeles, reported an association between a different variation in the gene and *a delay in the use of first words in children with autism* (Alarcon, Abraham, Stone, et al., 2008).

FOXP2 – the Curious Case of the Speech & Language Gene

- Finally, It is important to note that communication impairments associated with a variety of mutations of the FOXP2 gene are not simply the result of a fundamental deficit in motor control, and often include difficulties in comprehension and language formulation.
- It's also important to note that individuals with FOXP2 mutation also experience symptoms not related to language. Affected members of the KE family also evidenced oral motor dyspraxia, low nonverbal IQs, and nonverbal learning disorders. In other species, FOXP2 disruptions have been linked to digestive and growth disorders (certainly holding implications for syndromic patterns in some types of communication disorders).

FOXP2 – the Curious Case of the Speech & Language Gene

- Most importantly, it’s important to recognize the difference between heritable disorders and spontaneous mutations. Some cases, can be linked to a clearly inherited disorder, such as the FOXP2 mutation in the KE family resulting in DVD in a large percentage of family members. But for many disorders, such as a large majority of ASD cases, alterations/mutations are spontaneous, rather than being passed through families as an inherited feature, suggesting that different rare and possibly multiple mutations likely influence risk in different combinations - and in complex interplay with environmental factors.

Research in Brain Development:

AUTISM SPECTRUM DISORDERS - ETIOLOGY

Autism Spectrum Disorders

One of the best example of the variety of threats to communication development from interruptions or alterations in brain development can be seen with autism spectrum disorders. Research indicates that the etiology of interruptions or alterations in brain development resulting in ASD includes

- Genetic and Chromosomal abnormalities
- Metabolic Disorders
- Insult and/or injury
- Disease

Autism Spectrum Disorders

- As initially described by Kanner (1943), individuals with autism (now ASD) have three core features: (1) impairments in reciprocal social interactions; (2) an abnormal development and use of language; and (3) repetitive and ritualized behaviors and a narrow range of interests.
- In addition to the core features of autism, there are common co-morbid neurological disorders (DiCiccio-Bloom, et al., 2007). The prevalence of cognitive impairment in idiopathic autism is 60% although, when the autism spectrum is taken as a whole, the number is closer to 30%. Epilepsy has long been associated with ASD although estimates of the occurrence of seizure disorder vary from 5% to 44%. Anxiety and mood disorders are also very common in ASD.

Autism Spectrum Disorders

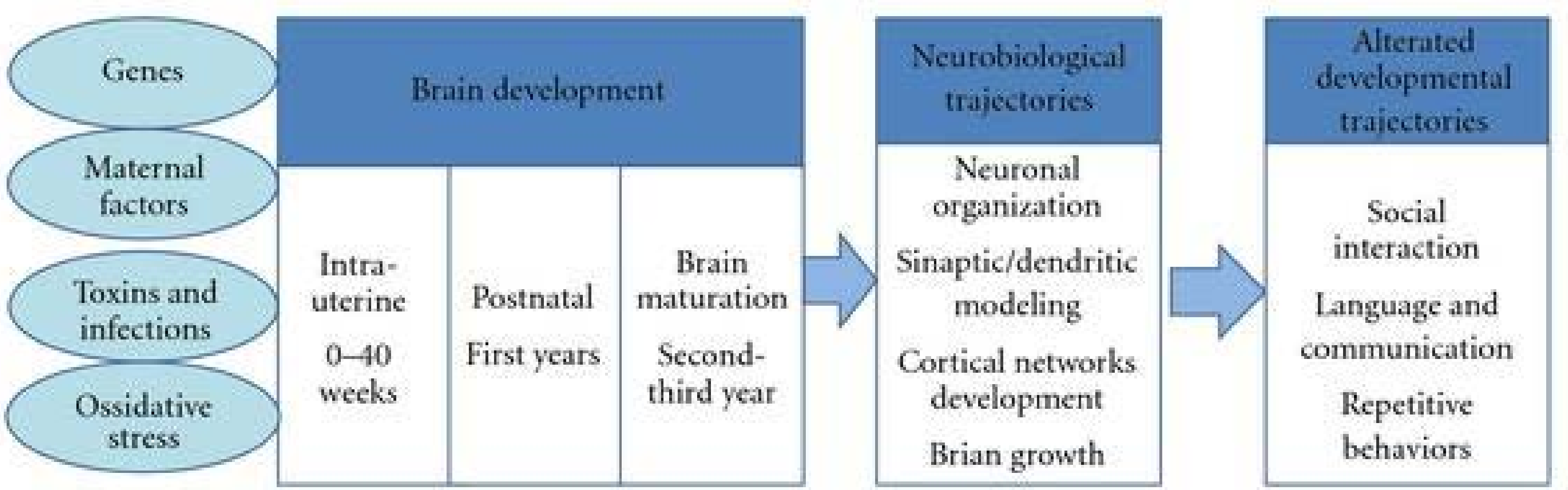
- There is also substantial heterogeneity in the onset of ASD. Some children have signs of developmental delays within the first 18 months of life. However, 25%–40% of children with ASD initially demonstrate near-normal development until 18–24 months, when they regress into an ASD pattern that is generally indistinguishable from early-onset ASD (Werner & Dawson, 2005).
- Rather than a single phenotype, it is more accurate to discuss “the autisms”, hence the use of the term *Autism Spectrum Disorders*; autism is a heterogeneous disorder with multiple causes and courses, a great range in the severity of symptoms, and several associated co-morbid disorders (Geschwind & Levitt, 2007).

Autism Spectrum Disorder

In the last decade, significant progress has been made in understanding the causes of autism spectrum disorders.

- **Several lines of evidences strongly support a prenatal onset for developmental abnormalities later leading to ASD**
- **Defined mutations, genetic syndromes, and metabolic diseases account for up to 20% of ASD patients.**
- **Metabolic and mitochondrial defects may have toxic effects on the brain cells, causing neuronal loss and altered modulation of neurotransmission systems.**
- **Fragile X-Syndrome and Tuberous Sclerosis Complex linked to ASD may reflect pathogenic alterations of the neocortical excitatory and/or inhibitory balance and perturbations in development of interneurons.**
- **Chromosomal abnormalities and potential candidate genes are strongly implicated in the disruption of neural connections, brain growth, and synaptic/dendritic morphology.**

Autism Spectrum Disorders



Genetic and epigenetic factors involved in the pathogenesis of autism. Interactions between multiple genes and environmental factors, such as intrauterine infections, alcohol/toxins exposure, and obstetrical suboptimality, can influence intrauterine and early postnatal brain development and disrupt crucial neurobiological pathways, from neuronal migration and cortical organization to synaptic and dendritic conformation, resulting in alterations of neurobehavioral trajectories that are involved in the pathogenesis of ASD (Benvenuto, Manzi, Alessandrelli, Galasso, and Curatolo, 2009).

Autism Spectrum Disorders

- Note: The majority of material for the next several slides comes from an excellent summary article in the International Journal of Pediatrics by Benvenuto, Manzi, Alessandrelli, Galasso, and Curatolo.

Chromosomal abnormalities in Autism/ASD: Chromosome 15

- According to Dykens, Sutcliffe, & Levitt (2004), **chromosomal rearrangements in 15q11-15q13 region** might be the most frequent cytogenetic abnormality in ASD. Within this region, **gamma-aminobutyric acid A receptor beta 3 (*GABA-ARB3)*, an inhibitory neurotransmitter receptor**, are currently thought to be central likely to play a significant role in the development of ASD, due to its role in neuronal inhibition and its expression in early development (Ma, Whitehead, Menold et al., 2005)
- A **chromosome 15 phenotype II**, characterized by ataxia, language delay, epilepsy, mental retardation, repetitive movement disorders, and facial dysmorphic features, has been described in individuals with chromosome 15 duplications (Shao, Curraco, Hauser, et al. (2003).

Autism Spectrum Disorders

Chromosomal abnormalities in Autism/ASD: Chromosome 7

- **Two of the loci most commonly associated with ASD by genetic linkage studies (7q22 and 7q31 regions) contain several genes implicated in the pathogenesis of autism** (Palferman, Matthews, Turner, et al., 2001; Yang & Gill, 2007) .
- The **RELN gene, found within the 7q22 region, has a pivotal role in neuronal migration and prenatal development of neural connections**, (Hong SE, Shugart YY, Huang DT, et al., 2000; Fatemi SH, Snow AV, Stary JM, et al., 2005) **and is potently inhibited by toxic substances, such as organophosphates (Quattrocchi CC, Wannenes F, Persico AM, et al., 2002).**

Autism Spectrum Disorders

Chromosomal abnormalities in Autism/ASD: Chromosome 7

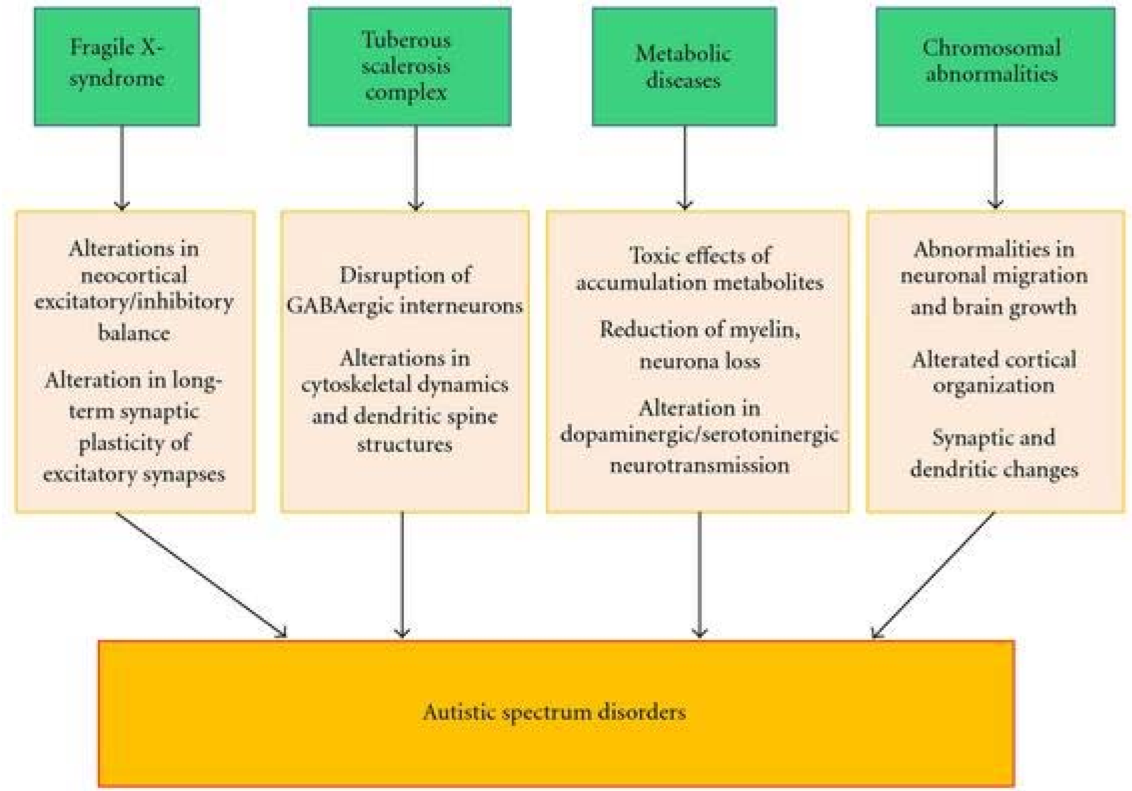
- Increased risk for autism can be also linked to a functional polymorphism in the **MET gene, found within the 7q31 locus** (Campbell, Sutcliffe, Ebert, et al., 2006), which plays a role into **development of the cerebral cortex & cerebellum**.
- **Williams-Beuren syndrome (WBS) region (7q11.23)** also contains several genes associated with **impairment in language and social interaction** (Meyer-Lindenberg, Mervis, & Faith Berman, 2006; Kirchhoff, Bisgaard, Bryndorf, & Gerdes, 2007) suggesting the existence of a **specific subgroup of ASD patients, characterized by dysmorphic features, mental retardation, language delay, congenital heart disease, and hypersensitivity to sound.**

Autism Spectrum Disorders

Chromosomal abnormalities in Autism/ASD: Chromosome 16

- An association between a **larger microdeletion on 16p11.2 and a syndrome that included developmental delay and distinct facial appearance** (hypertelorism, a broad nasal bridge and a broad nasal tip with a prominent columella, a short philtrum, long ears, a large mouth) has been described in the literature (Weiss, Shen, Korn, et al., 2008; Finelli, Natacci, Bonati, et al., 2004).
- **The chromosomal region 16p11.2 also encompasses the PRKCB1 locus, an interesting gene previously found associated with ASD** (Philippi, Roschmann, Tores, et al., 2005), and expressed in the **CNS, the immune system, the digestive tract, and the kidney**.

Autism Spectrum Disorders



Fragile X-syndrome

Tuberous scalerosis complex

Metabolic diseases

Chromosomal abnormalities

Alterations in neocortical excitatory/inhibitory balance

Alteration in long-term synaptic plasticity of excitatory synapses

Disruption of GABAergic interneurons

Alterations in cytoskeletal dynamics and dendritic spine structures

Toxic effects of accumulation metabolites

Reduction of myelin, neurona loss

Alteration in dopaminergic/serotoninergic neurotransmission

Abnormalities in neuronal migration and brain growth

Alterated cortical organization

Synaptic and dendritic changes

Autistic spectrum disorders

- *Potential pathogenetic mechanisms of syndromic autism.* Several medical conditions associated with syndromic autism appear to influence and potentially disrupt neurodevelopmental processes, including brain growth, cortical connectivity, and neurotransmitters pathways. These neurobiological alterations likely affect the developmental trajectory of social behavior and communication during early stages of childhood and determine the different clinical phenotypes of ASD (Benvenuto, Manzi, Alessandrelli, Galasso, and Curatolo, 2009).

Autism Spectrum Disorders

Metabolic Disorders

- In untreated children affected by phenylketonuria, **high levels of phenylalanine may have toxic effects on the brain cells, causing reduction of myelin, neuronal loss, and decreased levels of interneuronal connections** (Huttenloacher, 2000).
- Hyperphenylalaninemia also competes with the absorption of other amino acids, lowering tyrosine and tryptophan concentrations and resulting in a **low production of dopamine and serotonin in the prefrontal cortex** (Diamond, 1996).

Autism Spectrum Disorders

Metabolic Disorders

- **In severe metabolic diseases, like adenylosuccinase deficiency or creatine deficiency syndromes, neurological and behavioral symptoms are probably not caused by deficiency of metabolites, but are more likely due to the toxic effects of the accumulating substances on the brain** (Huttenloacher, 2000). **A direct role in modulation of dopaminergic and serotoninergic neurotransmission systems and axonal guidance has been hypothesized for the adenosine deaminase deficiency** as pathologic mechanisms for the development of altered pathways involved in ASD symptoms (Okada, Kawata, Murakami, et al, 1999).

Autism Spectrum Disorders

Fragile X Syndrome

- **Abnormalities in long-term synaptic plasticity of excitatory synapses and in baseline synaptic connectivity** may be the underlying neurological substrate of ASD associated with FXS (Bureau, Shepherd, & Svoboda, 2008; Selby, Zhang, & Sun, 2007).
- **Alterations in the neocortical excitatory/inhibitory balance as well as abnormal neural synchronization have been also reported in mouse model of FXS** (Gibson, Bartley, Hays, & Huber, 2008), resulting in hyperexcitability of neocortical circuits.
- **An immature dendritic morphology may also increase susceptibility to epilepsy and anxiety in FXS patients** (Pickett & London, 2005).

Autism Spectrum Disorders

Tubular Sclerosis Complex (TCS)

- **TSC is an inherited disorder resulting from mutations in one of two genes,** TSC1 (Hamartin) and TSC2 (Tuberin), **characterized by benign hamartomatous tumors that involve multiple organ systems**. It is **commonly associated with neuropsychiatric complications like epilepsy, mental retardation, ASD, and other behavioral problems**. Seizures can be present in the first year of life and up to one third of children develop infantile spasms. **Neurobehavioral phenotypes in TSC may arise from perturbations of interneurons development, which can selectively impact frontal and parietal areas** (Napolioni, Moavero, & Curatolo, 2009).

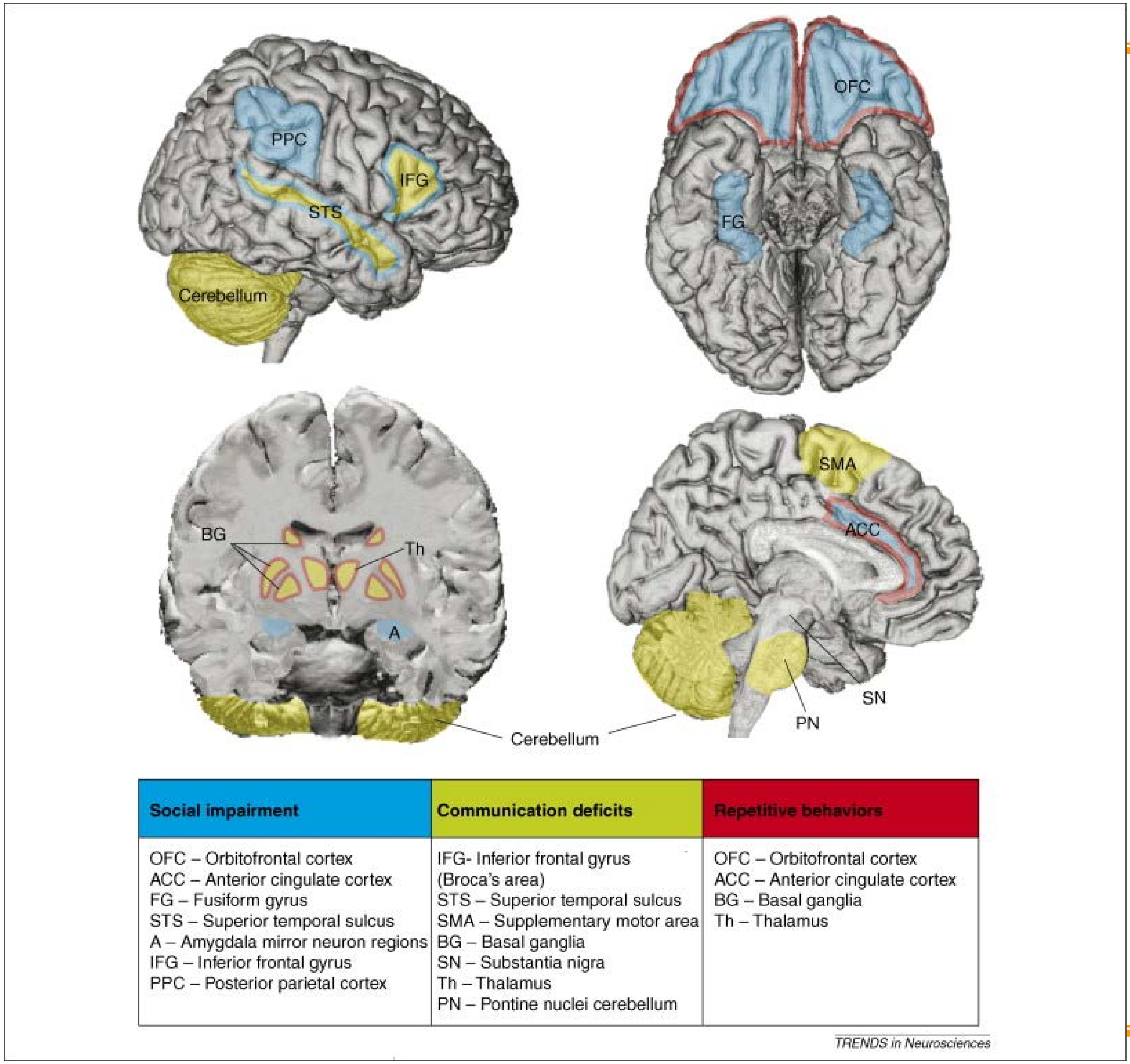
Research in Brain Development

AUTISM SPECTRUM DISORDERS: NEUROANATOMY

Autism Spectrum Disorders

- Because of the significant heterogenity seen within autism spectrum disorders, there is no single pattern of neuroanatomical differences that can be visualized as evidence of abnormal brain development within the population.
- It is possible, however, to look for differences in major brain regions that form the neural systems involved in the functions that are most impacted by the core features of autism. In a March 2008 article in Trends in Neuroscience, Amaral, Schumann, & Nordhal, using structural MRI analysis, provided some examples of possible neuroanatomical markers of abnormalities in brain development.

Autism Spectrum Disorders



Social impairment	Communication deficits	Repetitive behaviors
OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex FG – Fusiform gyrus STS – Superior temporal sulcus A – Amygdala mirror neuron regions IFG – Inferior frontal gyrus PPC – Posterior parietal cortex	IFG- Inferior frontal gyrus (Broca's area) STS – Superior temporal sulcus SMA – Supplementary motor area BG – Basal ganglia SN – Substantia nigra Th – Thalamus PN – Pontine nuclei cerebellum	OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex BG – Basal ganglia Th – Thalamus

TRENDS in Neurosciences

Brain areas that have been implicated in the mediation of the three core behaviors that are impaired in autism: (1) social behavior (blue areas), (2) language and communication (green areas), and (3) repetitive and stereotyped behaviors (red).

(Amaral, Schumann, & Nordhal, 2007)

Autism Spectrum Disorders

Differences in total brain volume

- One of the prominent theories of the neuropathology of ASD is that the brain undergoes a period of precocious growth during early postnatal life followed by a deceleration in age-related growth
- The evidence for this early overgrowth comes from studies of head circumference, a proxy for brain size, that provide evidence for normal or smaller head circumference (microcephaly) at birth followed by an increase in the rate of growth beginning at 12 months of age (macrocephaly).
- Existing MRI studies suggest that very young children with autism (ages 18 months to 4 years) have a 5%–10% abnormal enlargement in total brain volume. A recent 16 year longitudinal study across various ages indicated atypical age-related volumetric trajectories in ASD included enlarged gray matter volume in early childhood, an age-related increase in ventricle volume resulting in enlarged ventricles by early adulthood and reduced corpus callosum age-related volumetric increase resulting in smaller corpus callosum volume in adulthood. (Prigge, Lange, Bidler et al, 2021)

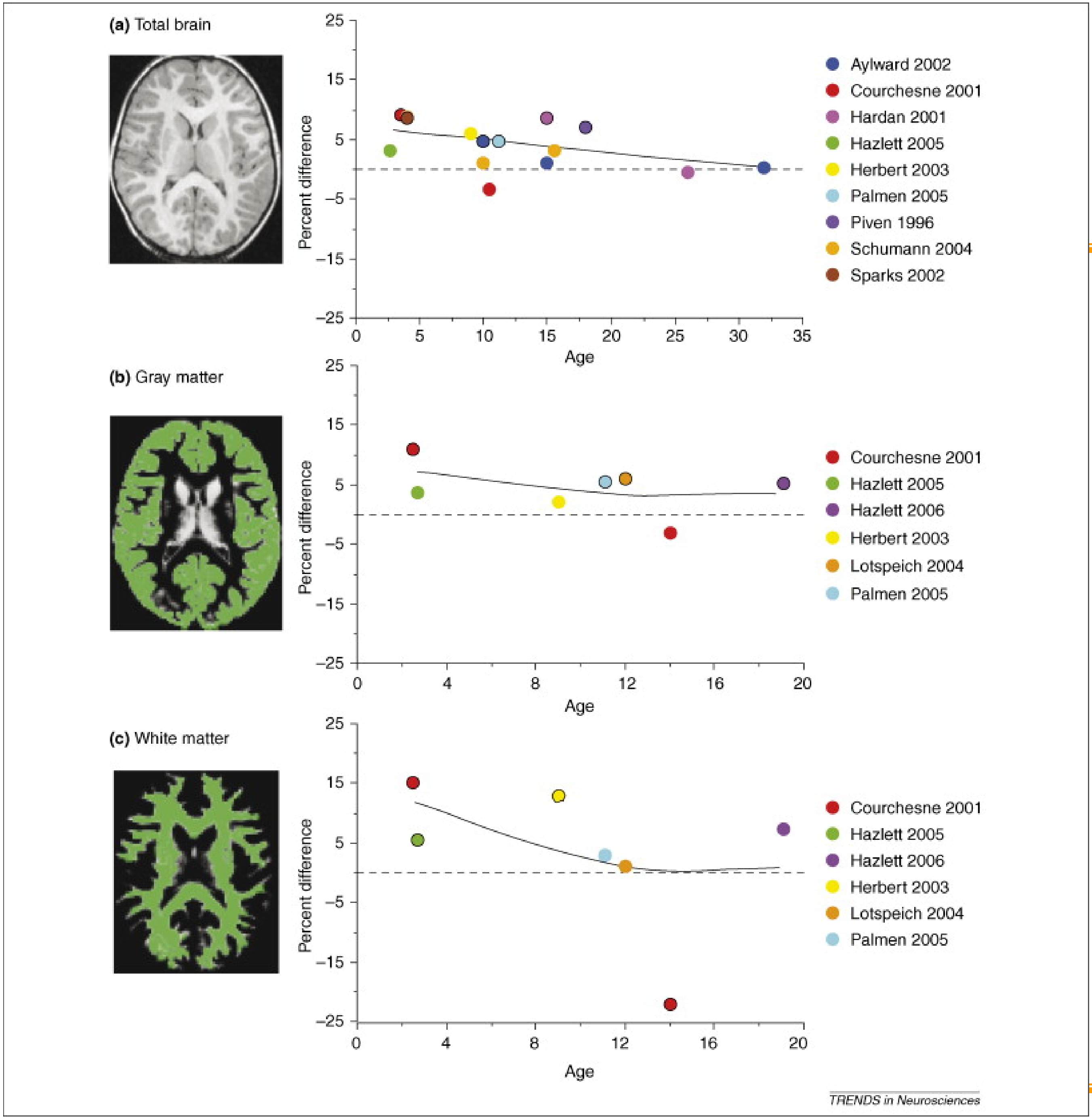


Figure illustrating differences in multiple research study outcomes on individuals with ASD for:

(a) total brain volume across age;

(b) gray matter volume across age;

(c) white matter volume across age.

- from Amaral, Schumann, & Nordhal (2007)

Autism Spectrum Disorders

Structural brain abnormalities and their association with language impairment in school-aged children with ASD

Gyrification, or cortical folding, in Autism Spectrum Disorder (ASD) is characterized by age-dependent and region-specific alterations, with findings suggesting increased gyrification in childhood that may be followed by a steeper-than-typical decline into adolescence and adulthood.

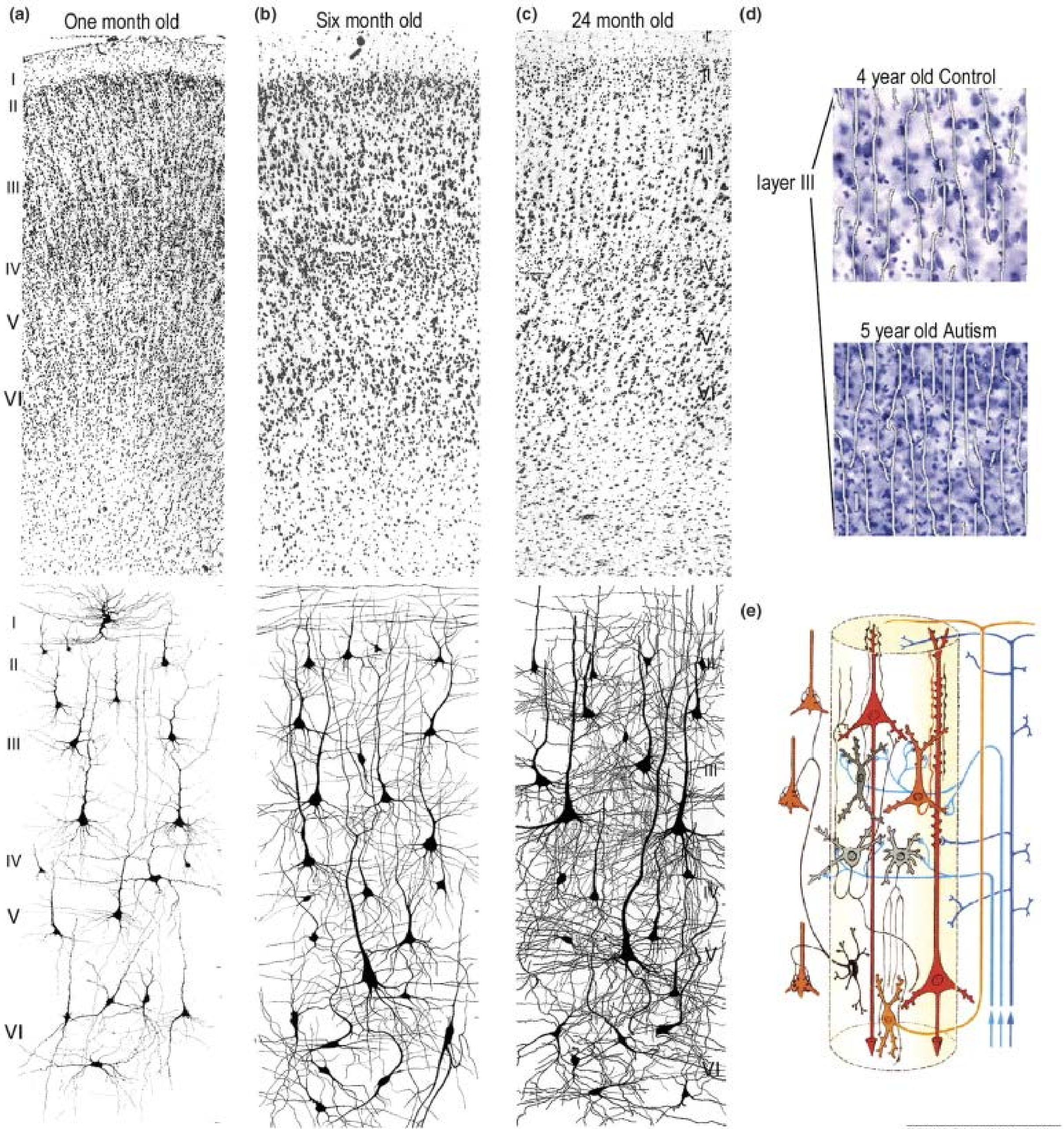
A 2023 study identified specific areas with altered gray matter (GM) volume and gyrification index (GI) in 18 schoolchildren with ASD and typically developing peers. The results demonstrated the pathological *decrease* of GM thickness in all language-related ROIs (transverse, superior, middle, and inferior temporal gyri; orbital, triangular, opercular parts of the inferior frontal gyrus and precentral gyrus; inferior parietal lobule) was associated with more severe language impairment. The pathological *increase* of GI in all these ROIs was also related to more severe language impairment in ASD.

(Arutiunian, Gomozova, Minnigulova, *et al.* 2023)

Autism Spectrum Disorders

Alterations of the columnar structure of the neocortex: minicolumn hypothesis

- Increasing interest has been placed on the notion, advanced by Casanova and colleagues (2002, 2006), that gray matter volume differences for ASD children may be affected by an abnormal number and width of minicolumns in individuals with autism. The neocortex is arranged in several layers/columns. The smallest column has come to be called the “minicolumn”. The minicolumn can be identified by the stacking of neuronal cell bodies, particularly in layers III and V of the neocortex.
- Only 14 cases of autism (9 of which had seizures and at least 10 with mental retardation) have been examined for minicolumnar pathology in cortical layer III in three independent studies using varying techniques. The most consistent finding in these studies is reduced intercolumnar width of the minicolumns (only layer III has been studied thus far) in dorsolateral prefrontal cortex or Brodmann's area (BA) 9. These findings, coupled with increases in neuronal density on the order of 23% noted by Casanova *et al.* (2006), imply that there should be a greater number of neurons in BA 9 of the autistic cortex. Given the narrower neuropil area between columns, one would also predict a decrease in the dendritic arborization of BA 9 neurons.



TRENDS in Neurosciences

- Illustration of neocortex structure potentially altered in ASD. a – c depicts cell body-stained sections of BA 9 at 1, 6 and 24 months of age. Below each is a representative Golgi-stained section showing the extent of dendritic growth in this same cortical area. By 2 years of age, the minicolumns are spaced farther apart with a lower cell density in a given region of cortex (from Amaral, Schumann, & Nordhal (2007)

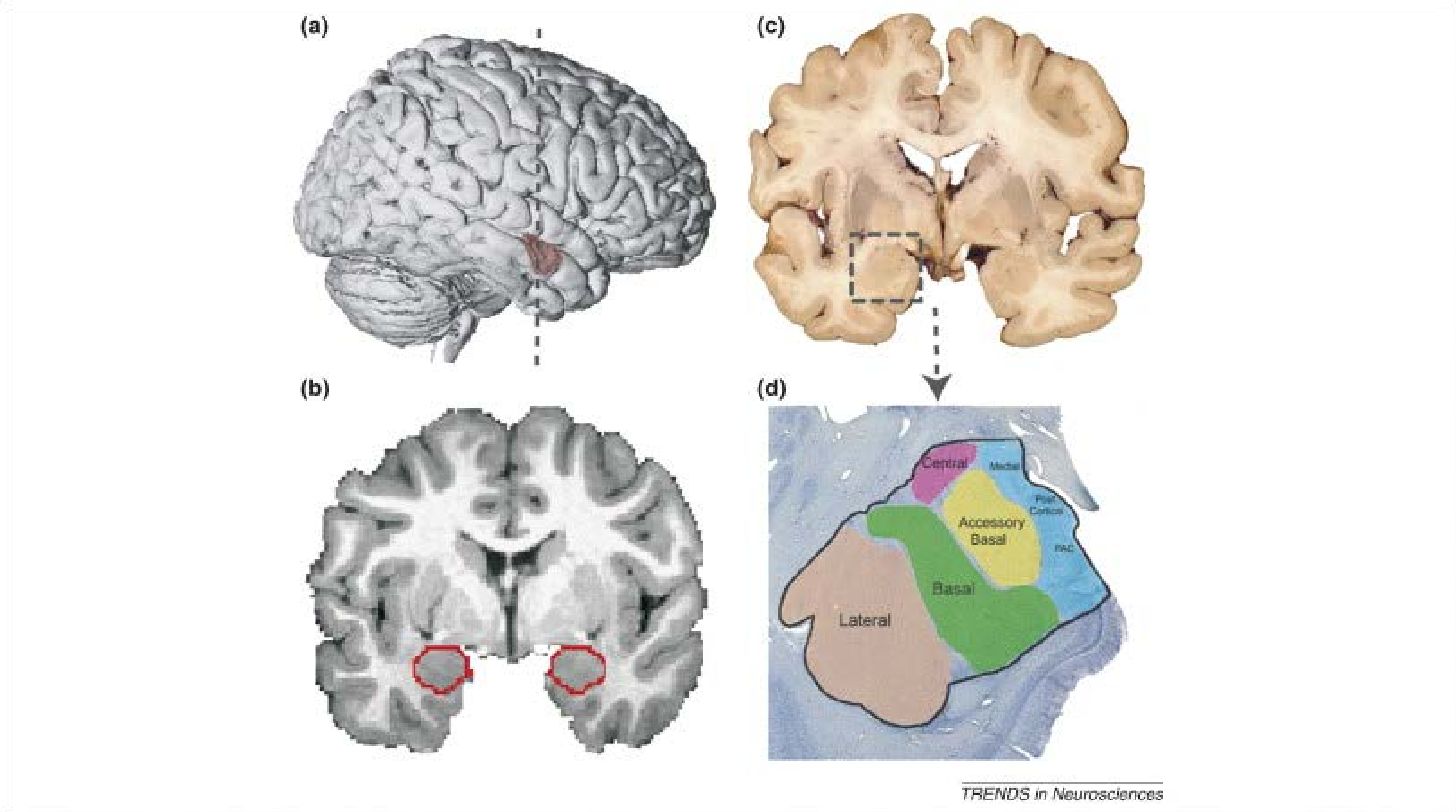
Autism Spectrum Disorders

Neuropathology of the amygdala

- The amygdala in boys with autism appears to undergo an abnormal developmental time course that includes a period of precocious enlargement that persists through late childhood. Sparks *et al.* (2002) found a 13%–16% abnormal enlargement of the amygdala in young children with autism (36–56 months of age). Recent studies suggest that amygdala enlargement is associated with more severe anxiety and worse social and communication skills.
- The amygdala appears typically sized initially in infancy with rapid overgrowth between 6-24 month of age, resultingly larger than normal in children with ASD, however, it does not undergo the same preadolescent age-related increase in volume that takes place in typically developing boys ending upto appear normal in size in adolescence. More recent research (Gibbard, 2017) reports abnormal enlargement continues into adulthood.

Autism Spectrum Disorders

Speech, Language, Hearing Sciences



Neuroanatomy of the human amygdala. (Amaral, Schumann, & Nordhal, 2007)

Research in Brain Development:

CHILDHOOD APRAXIA OF SPEECH (CAS)

Childhood Apraxia of Speech

Speech, Language, Hearing Sciences

Childhood apraxia of speech (CAS) is a neurological childhood (pediatric) speech sound disorder in which the precision and consistency of movements underlying speech are impaired in the absence of neuromuscular deficits (e.g. abnormal reflexes, abnormal tone). The core **impairment in planning and/or programming spatiotemporal parameters of movement sequences** results in errors in speech sound production and prosody – a "motor speech" disorder.

CAS may occur as a result of

- known neurological impairment,
- in association with complex neurobehavioral disorders of known and unknown origin, or
- an idiopathic neurogenic speech sound disorder. (ASHA 2007)

Also referred in research literature as: ***developmental apraxia of speech (DAS)***, ***developmental verbal dyspraxia (DVD)***, and as ***verbal dyspraxia*** in the DSM V

Childhood Apraxia of Speech

Common, but not necessary or sufficient for diagnosis:

- **Inconsistent errors** on consonants and vowels in repeated productions of syllables or words.
- **Lenghtened and disrupted coarticulatory transitions** between sounds and syllables.
- **Inappropriate prosody**, especially in the realization of lexical or phrasal stress (ASHA, 2007)

Childhood Apraxia of Speech

Other symptoms that help differentiate CAS from other SSDs:

- **articulatory groping -** articulatory searching prior to phonating
- **consonant distortions**
- **difficulty with smooth, accurate movement transitions from one sound to the next**
- **increasing difficulty with longer or more complex syllable and word shapes**
- **schwa additions/insertions -** insertion of schwa between consonants or at the end of words;
- **slower than typical rate of speech**
- **syllable segregation -** pauses between sounds, syllables, or words that affect smooth transitions;
- **voicing errors -** voiceless sounds produced as their voiced cognates; and
- **vowel errors -** vowel distortions or substitutions.

(ASHA, 2007; Iuzzini-Seigel (2017); Strand (2017)

Childhood Apraxia of Speech

CAS yields increased risk for problems in expressive language and weakness in the phonological foundations for literacy

- delayed language development
- expressive language problems, such as word order confusion and grammatical errors
- problems learning to read, spell, and write
- problems with social language/pragmatics.

(Lewis et al., 2004; McNeill, Gillon, & Dodd; 2009b)

Childhood Apraxia of Speech

Common co-occurring nonspeech sensory and motor problems:

- **gross and fine motor delays**
- **motor clumsiness**
- **oral apraxia**
- **limb apraxia**
- **feeding difficulties**
- **abnormal orosensory perception** (hyper- or hyposensitivity in the oral area).

(Crary & Anderson, 1991; Davis et al., 1998; Dewey, Roy, Square-Storer, & Hayden, 1988; McCabe, Rosenthal, & McLeod, 1998; Shriberg et al., 1997)

Childhood Apraxia of Speech

Speech, Language, Hearing Sciences

Brain Differences in Childhood Apraxia of Speech

- Children with idiopathic CAS were found to have normal structural brain MRI on conventional imaging, suggesting that brain abnormalities that underly idiopathic CAS might be too subtle to be detected by clinical MRI (Liegeois & Morgan, 2012).
- Emerging evidence from studies using more advanced quantitative measures of structural MRI in speech disorders support the presence of structural brain abnormalities on a microscopic level.
- Morphological abnormalities were found in **supramarginal gyrus** and **bilaterally in the planum temporale** and **in Heschl's gyrus** for children with a subtype of speech sound disorder characterized by persistent speech sound errors (Preston et al, 2014).
- In children with idiopathic CAS, a **thicker left supramarginal gyrus was found compared to controls** by (Kadiss et l, 2014), in the absence of appreciable macroscopic lesions.

Childhood Apraxia of Speech

Brain Differences in Childhood Apraxia of Speech

- Preston et al, (2014) and Fiori (2014) examining hemispheric interconnectivity found 3 subnetworks had altered (reduced) Fractional Anisotropy in children with CAS, compared to typically developing children.
- These networks included left inferior (opercular part) and superior (dorsolateral, medial and orbital part) frontal gyrus, left superior and middle temporal gyrus and left post-central gyrus (subnetwork 1); right supplementary motor area, left middle and inferior (orbital part) frontal gyrus, left precuneus and cuneus, right superior occipital gyrus and right cerebellum (subnetwork 2); right angular gyrus, right superior temporal gyrus and right inferior occipital gyrus (subnetwork 3).
- Reduced FA of some connections correlated with diadochokinesis, oromotor skills, expressive grammar and poor lexical production in CAS. The authors propose altered connectivity as a possible biological marker for CAS, to be considered in the diagnostic approach and possibly to be applied in the monitoring of changes induced by a specific rehabilitative intervention.

Research in Brain Development:

STUTTERING

Stuttering

- Stuttering is a disorder that typically begins in early childhood (50% of cases occur before the 4th birthday). There has long been a debate on whether it is a result of learning improper speech production patterns or of abnormal brain development.
- **Considerable neuroimaging research evidence exists**, from a variety of diagnostic sources including **structural (MRI)**, **hemodynamic (PET, fMRI, DTI)**, and **electrophysiologic (EEG, ERP, MEG) of altered brain patterns for receptive and expressive language in people who stutter (PWS)**.
- **The bulk of the evidence indicates a more diffuse language organizational structure with much greater right hemispheric representation, across a variety of cortical, subcortical &cerebellar sites**.
- This evidence is further supported by **a variety of physiologic measures** (diadochokinetic timing & accuracy, reaction time, articulatory and laryngeal kinematics) **showing abnormal performance in a percentage of PWS**.

Stuttering

Brain Structure and Physiology Differences linked to Stuttering

- Both children and adults who stutter show atypical brain structure and functional patterns that can be localized and form part of a number of major neural networks.
- Implicated are **cortical areas of the speech motor planning and control networks** including **frontal lobe regions: motor cortex**, **premotor cortex**, **inferior frontal gyrus (Broca)**, **frontal operculum**, **insular cortex**, and **presupplementary and supplementary motor areas**.
- Also implicated are **parietal and temporal perisylvian regions**, such as the **supramarginal gyrus**, and **higher order auditory regions**, which might be **related to differences in sensorimotor integration and feedback control**.
- Furthermore, **subcortical structures** such as the **basal ganglia**, **thalamus**, and **cerebellum** are implicated, which may relate to **differences in learning, initiation, timing, sequencing, & error monitoring functions**.

Stuttering

Brain Structure and Physiology Differences linked to Stuttering

- Morphological differences in **limbic brain regions involved in reward processing and emotion regulation**, such as the **nucleus accumbens** and **amygdala** are associated with persistent stuttering.
- Along with dysfunctional gray matter regions, alterations have also been reported for **white matter structures**, including the **arcuate fasciculus, superior longitudinal fasciculus, frontal aslant tract, corticobulbar tracts**, and **cerebellar penduncles**, which are responsible for **transmitting information between brain regions involved in speech production and motor control**.
- Comprehensive reviews of both state and trait markers of stuttering have been conducted and are available in the existing literature:

Neef, Anwander, Friederici, 2015; Watkins, Chesters, Connally, 2016; Budde, Barron, Fox, 2014;

Chang & Guenther, 2020; Craig-McQuaide, Akram, Zrinzo, Tripoliti, 2014; Chang S-E, Garnett EO, Etchell A, Chow, 2019

Stuttering

- The majority of the research, however, has been gathered on adult PWS, with little to no research conducted on young children near the instance that stuttering behavior is first noted.
- If these differences in brain structural morphology, metabolic and physiologic patterns in the brain, and also observed across a variety of behavioral measures reflect brain development differences that *cause* the disfluencies in speech *or are a result of* learned compensatory attempts to avoid or eliminate the disfluencies therefore cannot currently be answered.
- **One source for helping to answer that question has long been sought in the area of genetics. Stuttering appears to run in families in approximately 35% of cases. No clear genetic link had been revealed, although recently, karyotype and positional cloning studies in consanguineous families with abnormally large percentages of affected members had suggested possible regions of interest in several chromosomes**.

Stuttering

Genetic Findings with Stuttering

- A clear genetic marker for stuttering has been reported by Kang, Riazuddin, Mundorff, Krasnewich, Friedman, Mullikin and Drayna (2010). Drayna had previously led several of the researchers in identifying a significant linkage with **a locus on chromosome 12q** when studying blood relatives in 46 Pakistani families with stuttering.
- Drayna's group focused in on the largest family and found one or two copies of a **missense mutation in the *GNPTAB* gene**. **The GNPTAB gene is carried by all higher animals**, and helps encode an enzyme [alpha and beta catalytic subunits of GlcNac-phosphotransferase (TNPT)] that assists in breaking down and recycling cellular components, a process that takes place inside a cell structure called the lysosome. The mutation was found in all but three family members with stuttering.
- A few family members carried copies but didn't stutter, suggesting that the mutation increases risk but doesn't always result in stuttering,

Stuttering

Genetic Findings with Stuttering

- Further screening for mutations in *GNPTAB G3598A* was done in one unrelated individual with stuttering from the 46 original families along with 77 additional unrelated persons with stuttering from Pakistan, 96 unrelated controls without stuttering from Pakistan, and 270 affected, unrelated individuals and 276 unaffected matched controls from the U.S. & England.
- **The variant showed up in affected individuals in three other Pakistani families for a total penetrance of 10%. Only one control subject, an individual from Pakistan, carried the *GNPTAB* G3598A mutation**.
- **Three other mutations in *GNPTAB* were also seen in unrelated individuals with stuttering but not in controls. Three mutations in the related *GNPTG* gene (encodes the gamma rather than alpha and beta subunits of GNPT) appeared in both Asian and European study participants with stuttering but not in controls**.

Stuttering

Genetic Findings with Stuttering: Summary

- **Possibly up to 14 Chromosomes, with multiple regions:** 21q**, 20p, 18p, 18q, 16q** 15q**, 14q**, 13q, 12q**, 10q*, 9p, 9q*, 7q, 5q*, 3q**, 2q*, 2p** *(no asterisk – suggestive, * - significant, ** - highly significant)*
- GNPTAB on chromosome 12q (Riaz et al 2005) – 44 consanguineous (heavily intermarried) families in Pakistan; GNPTG & NAGPA (Kang et al, 2010, Raza et al, 2016) – functionally related genes to GNPTAB. All 3 are involved in lysomal enzyme encoding – management of waste proteins
- AP4E1 on chromosome 15 (Raza et al 2015) – consanguineous families in Cameroon (another protein encoding/transport gene)
- These 4 are thought to account for possibly 12% of stuttering cases, and it's unclear how their functional roles interrelate with speech production, except individuals with severest form show severe neurologic problems. Budde, et al, 2014 speculate they may result in incomplete myelinization.

Recent Research in Brain Development:

AUDITORY DISORDERS

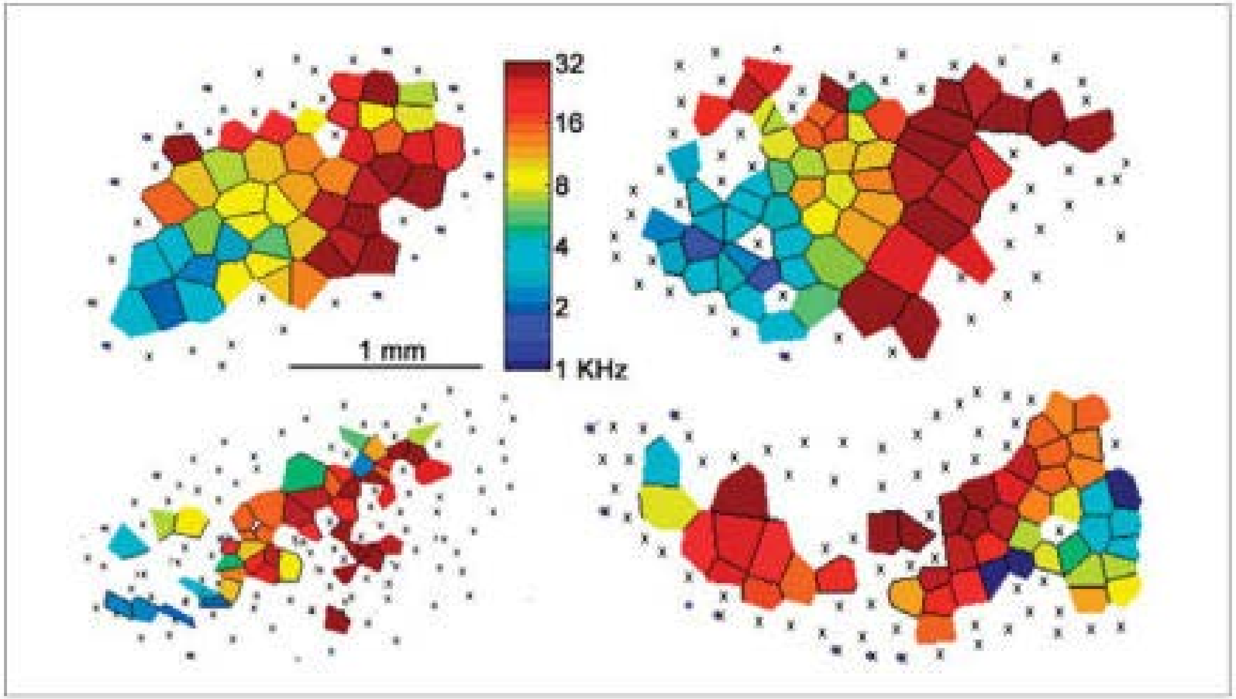
Auditory Disorders

- There are multiple genetic conditions resulting in auditory abnormalities, such as Wardenburg's syndrome.
- An recent article by Kenet et al. (2007) investigated the role of toxins (polychlorinated biphenyls – PCBs) affecting brain development resulting in auditory disorders.
- Kenet and colleagues at Harvard exposed rats to the non-coplanar polychlorinated biphenyl PCB95 during gestation and nursing. They noted a resulting abnormal development of the auditory cortex in the rats, affecting the brain's representation of what is heard.
- The researchers fed pregnant rats 6 mg/kg of PCB95 in corn oil daily from day 5 of pregnancy until the weaning of their pups and then mapped the boundary and response characteristics of the primary auditory cortex of the pups using a series of electrodes implanted in the brain. says Kenet.

Auditory Disorders

- Characteristic frequencies for individual auditory neurons were monitored during the mapping. The maps of the PCB95-exposed rats were found to be oddly shaped and had “holes” in them where neurons lacked responsiveness to auditory stimuli. The maps also included many neurons that showed a lack of frequency selectivity, and disorganization in the typical posterior-to-anterior distribution of neurons responding to increasing frequencies.
- In addition, the researchers recorded notable imbalances in inhibitory and excitatory signaling between the auditory cortex nerve cells. Without proper balancing, the correct representation of sound cannot be guaranteed. Kenet noted that these were similar to imbalances between excitation and inhibition in the brain observed inchildren with autism, but whether it’s the same type of imbalance remains to be explored.
- The researchers also found the plasticity of the PCB-exposed cortices to be abnormal.Typically, if rat pups are exposed to a particular tone, the area of the cortex that deals with that frequency expands, but did not occur in the PCB-exposed pups

Auditory Disorders



Top left shows a tonotopic map of the primary auditory cortex of a normal rat pup. At the left end of the map are neurons that are selective for low-frequency tones (blues); at the other end are neurons that respond only to high-frequency tones (reds). This pattern is usually smooth (i.e., no holes), continuous (gradually changing from one end to the other), and elliptical in shape. The other three examples above are from rats exposed to PCB95. These maps are neither continuous nor smooth, are very disorganized, and have erratic shapes (from Kenet et al., 2007).

Recent Research in Brain Development:

FINAL THOUGHTS

Implications for SLP and Audiolgy

General Thoughts

- Detection of brain development abnormalities underlying communication disorders is in it’s infancy.
- Much of the current research evidence and theories are built upon small numbers of cases, involve widely heterogeneous populations, and utilize divergent diagnostic methodologies, making it difficult draw clear evidence-based conclusions.
- Evidence developed with a particular diagnostic modality or methodality may not be supported by evidence gathered using a different modality or methodality.
- Identification of differences or abnormalities in brain development does not necessarily prove cause and effect; much is based on theory or deductive reasoning that may prove false.

Implications for SLP and Audiolgy

Diagnostic Challenges

- Communication disorders resulting from abnormal brain development offer many different and additional challenges diagnostically from those involving environmental or differential learning bases.
- The presence of syndromic features, such dysmorphism, presence of multiple cormorbid disorders, and co-occuring behavioral patterns may implicate the presence of abnormal brain development.
- Case history information, including familial patterns, prenatal, birth and developmental history, medical history and reports from other professionals, and reports of comorbid disorders may also assist in identification.
- Brain developmental differences or abnormalities yielding more unitary symptoms, e. g., mild to moderate SLI, will be much harder to identify than those evidencing multiple symptoms, yet still affect treatment outcomes.

Implications for SLP and Audiolgy

Speech, Language, Hearing Sciences

Treatment/Management Challenges

- It is logical to assume that a linkage of a disorder to brain abnormalities or differences rather than learning or environment implies a greater challenge to the clinician, a less satisfactory response to traditional techniques from the client, and less favorable outcomes. There is, however, little current evidence to support this.
- Long term minimal or unfavorable client response to typical evidenced-supported treatment strategies for the identified communication disorder symptom should merit clinician-investigation of brain development abnormalities as a possible alternative source of the symptom.
- Case management for individuals with communication disorders resulting from brain development abnormalities or differences may benefit from gathering different (additional) data on individual performance, trying a variety of treatment methods, or seeking additional professional input.
- Multidisciplinary team approaches may be more appropriate and beneficial.