Research in Brain Development: Implications for Speech & Language Disorders

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My Predicament

- How to organize a talk on recent research findings in brain development – so much has been done!
  - Advances in understanding complexity and diversity of gestational and childhood anatomical development
  - Advances in understanding genetic influences on development
  - How recent technological innovations have contributed to understanding brain development, such as genomic analysis, transcriptome analysis, fMRI, DTI, ERP/MEG
  - Advances in understanding how differences in brain development contribute to specific communication disorders (ASD, SLI, Stuttering, Auditory Disorders)
  - Implications for practice of speech-language pathology
Inter-operative neural stimulation is one technique used to explore the link between brain anatomy and brain function.
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”
  - Developmental apraxia of speech/devel. verbal dyspraxia
  - Specific language impairment
  - Autism spectrum disorders
  - Stuttering
- Implications for speech-language pathology and audiology
How the brain works
Recent Research in Brain Development:

NORMAL PATTERNS OF BRAIN DEVELOPMENT
Brain Development: Embryonic

- Early in an embryo’s development, a strip of specialized cells called the notochord (A) induces the 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) Mouse embryo at 10 days (5 weeks in human)

(b) A midsaggital cut through the recently closed cranial neural tube illustrates the **forebrain**/prosencephalon (telencephalon/diencephalon), **midbrain**/mesencephalon (diencephalon), and **hindbrain**/rhombencephalon (metencephalon/mylencephalon).

(http://www.med.unc.edu/embryo_images/unit-nervous/nerv_htms/nervtoc.htm)
Brain Development: Embryonic

After 11 weeks, the expanding cerebral hemispheres have overgrown the diencephalon. At the metencephalon, cortical formation and expansion produce the cerebellum, which overlies the nuclei and tracts of the pons.
Gestational Brain Development
Brain Development: Gestational

- The development of the human brain is a dynamic process that continues throughout gestation. In the early gestational period, basic CNS structural development and neural proliferation and dissemination occur. Later gestational stages center on corticofugal neurogenesis - the process of neural development and the connectivity between the various layers of the brain (Leviton and Gressens, 2007; Johnson, et al, 2009).

- 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 (Adams-Chapman, 2006; Kinney, 2006). 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. Serial MRI imaging of the developing preterm brain graphically illustrate the evolution of this fascinating process (Kapellou et al, 2006) – next slide.
Brain Development: Gestational

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

- Matthew Johnson and his colleagues at Yale and UCLA (2009) recently supplied another fascinating piece to the puzzle in understanding the complexity and diversity of gestational brain development, especially in relation to speech and language area development. They conducted global transcriptome analysis on 4 late mid-fetal human brains (18, 19, 21, & 23 weeks gestational age). Global transcriptome analysis examines RNA rather than DNA (genome analysis), and provides a method for examining the processes of cell differentiation, vital in understanding the massive changes taking place in fetal brain development. It also provides a better understanding of how protein regulation impacts gene expression and thus neuronal formation and connectivity, leading to specific disorders, such as autism. They also compared their results to other cross species transcriptome analyses.

- Johnson et al examined the transcriptome of the left & right cerebellum, thalamus, striatum, hippocampus, and 9 neocortical areas, several of which are directly linked to speech and language.
Brain Development: Gestational

- Among their results (Johnson et al) were clear indications of altered gene regulation in the human brain, accelerating growth and development of the prefrontal cortex (e.g., Broca’s area and homologous area on other side) and perisylvian area (e.g., planum temporale, Wernicke’s area) vs. that seen in non-human primate brains.
- Johnson also found molecular influences leading to the left vs. right interhemispheric asymmetries in the perisylvian area/planum temporale were still operating at the late mid-fetal stage.
- They further demonstrated that genes enriched in the prefrontal cortex area and motor-somatosensory neocortex area included FOXP2, which we shall discuss shortly. Insufficiency of FOXP2 causes a severe speech and language disorder associated with morphological abnormalities and functional underactivation of Broca’s area.
- Most striking was the vast diversity of gene expression observed at this late mid-fetal stage, with significant implications for better understanding a wide variety of communication (and other) disorders.
Brain development: Birth – 2 years

- Knickmeyer, Gouttard, Kang, et. al. (2008) utilized a Siemens head-only 3T MRI scanner to structurally examine the brains of 98 children: 84 children at 2–4 weeks of age, 35 at 1 year and 26 at 2 years of age.

- Total brain volume increased 101% in the first year, with a 15% increase in the second. The majority of hemispheric growth was accounted for 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. The caudate increased 19% and the hippocampus 13% from age 1 to age 2.
Brain development: Birth – 2 years

- 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 are taking 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, 1, and 2 years. 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

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

(From Knickmeyer, Gouttard, Kang, et al., 2008)
Increase in neuronal density and synaptic connectivity from birth to two years. The brain increases from \( \frac{1}{4} \) the size of the adult brain to \( \frac{4}{5} \) adult size, due to a large extent from increases in axonic and dendritic connectivity.
Human Brain Development

Neural Connections for Different Functions Develop Sequentially

Sensory Pathways (Vision, Hearing)

Language

Higher Cognitive Function

FIRST YEAR

-8 -7 -6 -5 -4 -3 -2 -1 1 2 3 4 5 6 7 8 9 10 11

Birth (Months) (Years)

Anatomy of a Teenager's Brain

- Embarrassed by parents section
- Ability to remember the lyrics to offensive hip hop song...
- Have no idea...
- Cars, cars, cars, cars, and oh, yeah, girls...
- Girls are suddenly fascinating section
- Ability to listen to extremely loud base tracks
- School Work (smallest section of the brain)

Sensorimotor area
Random Information

How the brain works: male vs. female
Rapid and Dynamic Brain Development: Implications

The act of communication, from auditory and visual reception of communication signals, through processing, reasoning, and response formulation (on multiple levels) and finally 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
Recent Research in Brain Development:

IDENTIFYING GENES FOR COMMUNICATION DISORDERS
Determining if a particular speech, language, or hearing disorder has a genetic basis involves a multistep process of increasingly narrow scope (adapted from Gibson & Gruen, 2008)

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

- 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.
2. 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
- FOXP2 first identified with karotype analysis
- Karotype analysis incapable of examining DNA sequences
3. Genetic Linkage analysis

- Determines the chromosomal regions that contribute to the development of the trait/disorder, traditionally 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) typically 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).
4. Genetic Association studies (positional cloning)

- Narrow scope/in-depth look at specific susceptibility loci identified in genetic linkage studies

- These 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.
5. 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).
Recent 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.
- 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

- Interestingly, 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, and 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

- 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. Enard, Przewarski, Fisher et al (2002) have speculated that the two amino acid differences between chimps and humans led to the evolution of language in humans, although Scharf and Haesler (2004) find little to support this hypothesis.

- 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 – the Curious Case of the Speech & Language Gene

- In 2003, Lai, Gerelli, Monaco, Fisher, and Copp reported finding 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 the original FOXP2-related speech and language disorder (developmental verbal dyspraxia).

- 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 DVD 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 researchers 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).
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 autism spectrum disorder (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.
Recent Research in Brain Development:

AUTISM AND AUTISM SPECTRUM DISORDERS - ETIOLOGY
Autism and 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 and autism spectrum disorders. Research indicates that the etiology of interruptions or alterations in brain development resulting in autism or ASD includes:

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

- As initially described by Kanner (1943), individuals with autism 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 mental retardation 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 autism, although estimates of the occurrence of seizure disorder vary from 5% to 44%. Anxiety and mood disorders are also very common in autism.
Autism and Autism Spectrum Disorders

- There is also substantial heterogeneity in the onset of autism. Some children have signs of developmental delays within the first 18 months of life. However, anywhere from 25%–40% of children with autism initially demonstrate near-normal development until approximately 18–24 months, when they regress into an autism that is generally indistinguishable from early-onset autism (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 and Autism Spectrum Disorders

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

- Several lines of evidences strongly support a prenatal onset for developmental abnormalities later leading to autism.
- Defined mutations, genetic syndromes, and metabolic diseases account for up to 20% of autistic patients.
- Metabolic and mitochondrial defects may have toxic effects on the brain cells, causing neuronal loss and altered modulation of neurotransmission systems, resulting in autistic behavior.
- Fragile X-Syndrome and Tuberous Sclerosis Complex subtypes may reflect pathogenic alterations of the neocortical excitatory/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 and 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 and Autism Spectrum Disorders

- Note: The majority of material for the next several slides comes from an excellent 2009 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 and 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 susceptible to inhibition by toxic substances, such as organophosphates (Quattrocchi CC, Wannenes F, Persico AM, et al., 2002).
Autism and 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 in development of the cerebral cortex and 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 autistic patients, characterized by dysmorphic features, mental retardation, language delay, congenital heart disease, and hypersensitivity to sound.
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 autism (Philippi, Roschmann, Tores, et al., 2005), and expressed in the CNS, the immune system, the digestive tract, and the kidney.
Autism and Autism 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 and 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 (Huttenlocher, 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), which results in distinct patterns of communication impairment and personality abnormality.
Autism and 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 autistic symptoms (Okada, Kawata, Murakami, et al, 1999).
Autism and 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 autism 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 and 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, autism, 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).
Recent Research in Brain Development

AUTISM AND AUTISM SPECTRUM DISORDERS: NEUROANATOMY
Autism and Autism Spectrum Disorders

- Because of the significant heterogeneity seen within the 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.
Brain areas that have been implicated in the mediation of the three core behaviors that are impaired in autism: (1) social behavior, (2) language and communication, and (3) repetitive and stereotyped behaviors (Amaral, Schumann, & Nordhal, 2007)
Autism and Autism Spectrum Disorders

Differences in total brain volume

- Currently, one of the most prominent theories of the neuropathology of autism is that the brain undergoes a period of precocious growth during early postnatal life followed by a deceleration in age-related growth (Courchesne et al., 2003). The evidence for this early overgrowth comes from four studies of head circumference, a proxy for brain size, that provide evidence for normal or smaller head circumference at birth followed by an increase in the rate of growth beginning at 12 months of age. 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, but whether this enlargement persists into later childhood and adolescence is not as clear (Amaral, Schumann, & Nordhal, 2007).
Figure from Amaral, Schumann, & Nordhal (2007) illustrating differences in research study outcomes for (a) total brain volume across age; (b) gray matter volume across age; and (c) white matter volume across age.
Autism and Autism Spectrum Disorders

Involvement of gray vs. white matter in volume differences

- Another prominent theory, postulated by Herbert et al. (2003), is that the abnormal brain enlargement observed in children with autism is disproportionately accounted for by increased white matter, not gray matter. Indeed, two studies of very young children (1.5–4 years) show greater increases in white matter than gray matter (see prior figure). But again, whether these increases persist into later childhood and adolescence is less clear.

- Existing evidence on gray matter volume suggests that although gray matter enlargement might be proportionately smaller than white matter enlargement early in life, the enlargement might persist into adulthood. Four studies, collectively spanning early childhood through adolescence and adulthood, report 6%–12% enlargement of gray matter.
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 there are 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.
Illustration of neocortex structure potentially altered in autism. 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))
Neuropathology of the amygdala

- In humans the amygdalae perform primary roles in the formation and storage of memories associated with emotional events. Research indicates that during fear conditioning, sensory stimuli reach portions of the amygdala, where they form associations with memories of the stimuli.

- 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 initially to be larger than normal in children with autism, but does not undergo the same preadolescent age-related increase in volume that takes place in typically developing boys.
Autism and Autism Spectrum Disorders

Neuroanatomy of the human amygdala. (Amaral, Schumann, & Nordhal, 2007)
Recent 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 and cerebellar sites.

- This evidence is further supported by a variety of physiologic measures (diadochokinetic timing & accuracy, reaction time, articulatory and laryngeal kinematics, etc.) showing abnormal performance in a percentage of PWS.
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

First Clear Genetic Linkage in stuttering

A number of recent genetic studies utilizing families with a high incidence of members who stutter have identified possible genetic linkages to stuttering.

- Shugart et al (2004), in a study with 68 families from North America and Great Britain, reported a high heredity score, but that did not reach the level necessary for genome wide statistical significance, for chromosome 18.

- In 2006, a group from the Illinois International Genetics of Stuttering Project, utilizing 100 families where at least 2 members stuttered, reported a sex-specific linkage on chromosome 7 for males, and on chromosome 21 for females. Additional suggestive linkages were reported on chromosome 9 and on chromosome 15, depending on how stuttering members were combined.

- In a follow-up study using one large Hutterite family, Wittke-Thompson et al (2007) reported nominally significant linkages with chromosomes 3, 13, and 15, and when pooled with the earlier Illinois data, for chromosomes 2 & 5.
Stuttering

- In a study of 44 consanguineous families in Pakistan, Riaz et al (2005) reported finding a genomic linkage to stuttering for chromosomes 1, 5, and 7, with the strongest and most significant linkage noted for a marker in chromosome 12.

- In a follow-up to the Riaz familial study, Kang et al (2010), focused in on the largest family and found one or two copies of a missense mutation in the GNPTAB gene in chromosome 12. 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.

- Two of the family members carried two copies and one carried one copy of the mutation but didn't stutter, suggesting that the mutation increases risk but doesn't always result in stuttering,
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. and 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

- Three more mutations were seen in the \textit{NAGPA} gene, which encodes another enzyme in the same pathway, again in affected individuals but not controls.

- The results implicate a class of genes in the same pathway that encode enzymes that generate the mannose-6-phosphate signal, which directs a diverse group of hydrolases to the lysosome. Lysosomes are found in most cell types where they act as the "garbage bag" for waste products broken down by the hydrolase enzymes.

- Failure of this pathway is known to result in the rare but fatal disorder mucolipidosis type II, and other lysosomal storage disorders that typically affect bone, connective tissue, and neurologic function.

- It’s important to note that while the results do support abnormalities in brain development as being implicated in stuttering, taken altogether, the 3 gene variants accounted for 5% (21 of 393) of stuttering cases in unrelated persons.
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 in children 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 its 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 to draw clear evidence-based conclusions. Because of ethical constraints, much of the research involves animal models, rather than human.
- Evidence developed with a particular research 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.
Anatomy of the Cat Brain
Much of brain development research comes from animal models, which have different brain function.

“The prefrontal cortex is involved in higher mental functioning, like using a can opener and remembering to feed you.”
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 comorbid disorders, and co-occurring 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.
Random Information

For some individuals, it’s relatively easy to figure out what is different in brain organization, and to verify causality.
Random Information

The success of higher order functions can differ widely among individuals.
Implications for SLP and Audiology

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.
Parting thoughts

"Mr. Osborne, may I be excused? My brain is full."