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Genetic and Neurological Correlates of Childhood Apraxia of Speech

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Moderated By:

Amy Hansen, M.A.,CCC-SLP, Managing Editor, SpeechPathology.com

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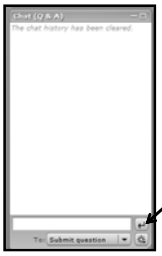

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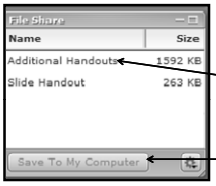

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GENETIC AND NEUROLOGICAL CORRELATES OF CHILDHOOD APRAXIA OF SPEECH

Barbara Lewis, Ph.D.
Department of Communication Sciences
Case Western Reserve University
October 14, 2010

INTRODUCTION

- Recent studies have suggested a genetic etiology for some SSD and have linked candidate chromosome regions to specific cognitive processes or endophenotypes. Candidate genes, residing within these chromosome regions, are known to influence neural development.
- Identification of the relationship of phenotypes, genes and neurological processes will improve our understanding of the neural basis of speech sound production and allow us to identify processing differences and deficits in individuals with SSD.

INTRODUCTION CONTINUED

- Ultimately, it is hoped that therapy may be tailored to address specific component skills associated with different processing deficits. The effects of therapy may be tracked through neuroimaging techniques as has been demonstrated for dyslexia.

TOPICS FOR DISCUSSION

- Review of genetics
  - Justification for genetic study
  - SSD as a complex trait
  - Challenges
- Genetic studies to date
  - Types of genetic studies
  - Linkage studies
  - Candidate Genes for idiopathic CAS
  - Syndromes associated with CAS
- Evidence from fMRI studies
- Future Directions

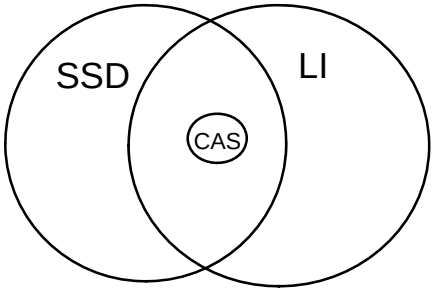
JUSTIFICATION FOR GENETIC STUDIES

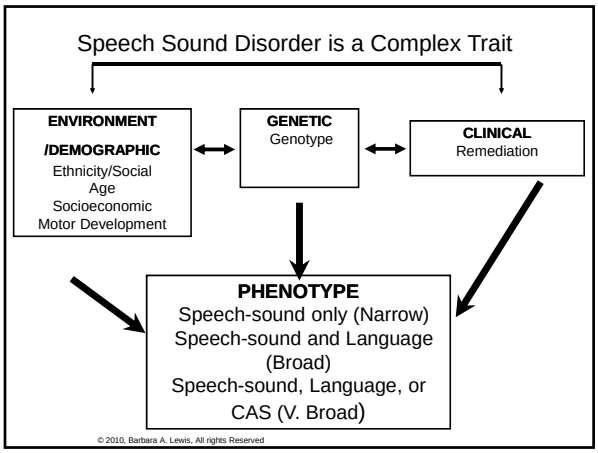
- Early identification of those at risk, allowing for environmental intervention at a young age.
- Understanding of molecular pathology to shed light on normal processes of speech and language.
- Identification of key genetic pathways; that is, proteins that genes code and the resulting metabolic, structure, signaling, transcriptional regulation, or other cellular pathways.
- Bridging the gap between brain imaging and neuropsychology, for a comprehensive understanding of disorders.

JUSTIFICATION FOR GENETIC STUDIES (CONTINUED)

- Current diagnostic categories based on behavioral observations may be validated.
- New diagnostic categories based on genetic information may be established.
- Therapy techniques may be tailored to fit the underlying genetic basis.
- Understanding of the cognitive overlap of comorbid disorders of language impairment, reading disorders, spelling, ADHD, learning disabilities
- Evolutionary considerations

CO-MORBIDITY OF SSD, LI AND CAS





SOME GENETIC CONSIDERATIONS WHEN STUDYING A COMPLEX HUMAN TRAIT

- No single gene is responsible for the majority of cases or deficit of any particular developmental disorder.
- Multiple heterogeneous effects of risk genes may act alone or together to give rise to multiple profiles of skills, culminating in the same diagnosis and general impairment on the surface.
- A single genetic defect may result in multiple problems if it is present early in development.

SOME GENETIC CONSIDERATIONS WHEN STUDYING A COMPLEX HUMAN TRAIT (CONTINUED)

- Different components of this complex phenotype could be linked to distinct genetic loci.
- Nature and severity of the disorder might vary at different developmental stages; genes may be turned on and off during the life span.
- Environmental effects may be unique to individuals (non-shared environment). Identifying broad encompassing effects will be difficult.

CHALLENGES OF GENETIC STUDIES OF SPEECH AND LANGUAGE DISORDERS

- Lack of lifespan measures
  - Reliance on historical reports
- Developmental changes in the phenotype
  - The "vanishing phenotype"
- Environmental correlates are not understood
  - Parents with a disorder may provide a deviant linguistic environment

PROBLEMS WITH GENETIC STUDIES OF SPEECH AND LANGUAGE DISORDERS

- Lack of clear phenotypic boundaries
  - Comorbid conditions include reading disorders, ADHD, mental retardation, learning disabilities
  - Numerous biochemical and physiologic processes and anatomical structures
  - Specific cognitive skills may be differentially heritable and each contribute to speech and language
  - Ascertainment bias: studies recruit from clinical populations.
  - Mouse models?

GENETIC STUDIES

The role of endophenotypes

GENETICS 101

- Genome- complete set of DNA in an organism
- Chromosomes- 24 Human chromosomes that are numbered from largest (chromosome 1) to smallest (Y chromosome)
- Genes- on chromosomes code for proteins; humans have 20,000-25,000 genes
- Proteins are large complex molecules made up of amino acids that define the function of a cell
- Proteome- all the proteins in a cell
- DNA sequencing- the process of determining the exact order of the base pairs that make up the 24 chromosomes of humans

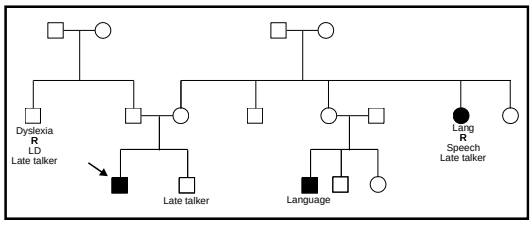
STRUCTURE OF A CHROMOSOME

- Centromere- structure that joins two strands of the chromosome
- p arm - the short arm or chromatid
- q arm - the long arm or chromatid
- bands - alternating regions of dark and light that appear when stained
- genes - segments of DNA contained on the chromosome

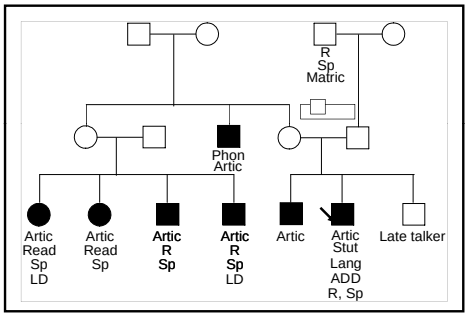
QUESTIONS ANSWERED BY GENETIC STUDIES

QUESTION	*STUDY TYPE*
Is the disorder familial?	Family Study
Is the disorder inherited?	Twin and Adoption study
How is the disorder inherited?	Segregation and pedigree studies
Where is the gene?	Linkage analysis
What is the genetic defect?	Molecular Analysis

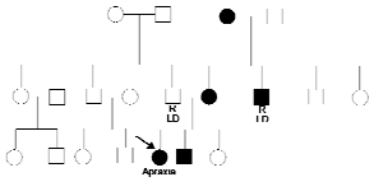
PEDIGREE OF PHONOLOGY ALONE PROBAND



PEDIGREE OF PHONOLOGY + LANGUAGE PROBAND



PEDIGREE OF APRAXIC PROBAND



Proband is severely apraxic
Brother is in speech therapy.
Father is dyslexic and learning disabled
Mother had speech therapy.
Both mother and maternal grandmother were
not understood until age 5
Maternal uncle had speech therapy and was dyslexic.

K.E. FAMILY

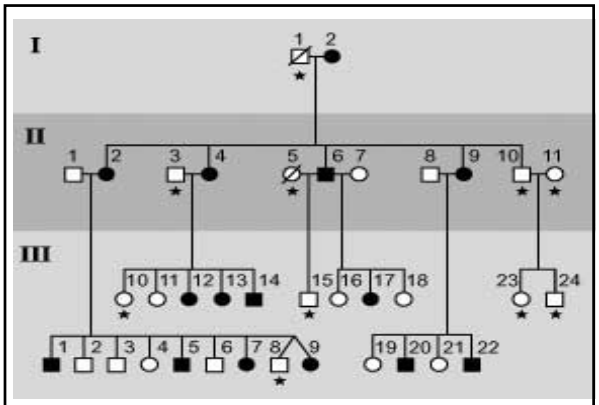
- British family of Pakistani origin, 4 generations, (Hurst et al., 1990)
- 37 members with 15 members affected
- Abnormal *FOXP2* gene on chromosome 7
- Gene produces protein known as a transcription factor that binds directly to DNA and regulates other genes, including genes that influence language areas in the brain; Example: *FOXP2* influences *CNTNAP2* (Vernes et al, 2008), a gene associated with language disorders and autism.
- Brain imaging studies of KE family revealed structural and functional abnormalities

BRAIN IMAGING STUDIES OF KE FAMILY

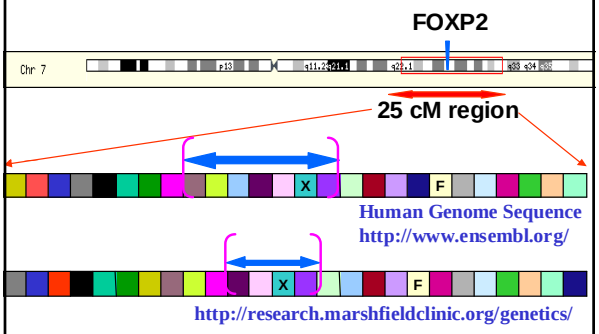
- Abnormalities in cerebellum and striatum
- Reduced gray matter densities in caudate nucleus, the cerebellum, the inferior frontal gyrus, and lower primary motor cortex
- During language tasks, affected members show bilateral, diffuse activation, with little or no activity in left inferior frontal cortex (Broca's area) and reduced activity in other speech-related cortical and subcortical brain regions.
- Over-activation was observed in posterior parietal, occipital, and post central regions (not typically activated during speech).

PHENOTYPES IN KE FAMILY

- Verbal dyspraxia
- Expressive and receptive language deficits
  - Grammatical deficits
- Poor non-word repetition
- Written language deficits
- Cognitive impairments
- Oral facial praxis
- Procedural learning/memory deficit

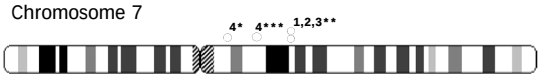


Resolution of problems with marker order



http://research.marshfieldclinic.org/genetics/

Chromosome 7



* 7q11.22;AUTS2 autism susceptibility candidate 2
** 7q31;FOXP2
*** Language delay in one of three relatives w/o ASD; 46, xy, t(1:7)(p22:q21) balanced paternal translocation

1 Dyslexia
2 Speech Sound Disorder
3 Language Impairment
4 Autism Spectrum Disorder

- Association
- Linkage
- Chromosomal Abnormality

OTHER INDIVIDUALS WITH *FOXP2* ABNORMALITIES

- Point mutation (different from KE family) in 2 sibs and mother with speech production difficulties (MacDermot et al, 2005)
- Balanced translocation involving *FOXP2* region presented with severe oral facial apraxia (Lai et al.,2001)
- Deletion of *FOXP2* region- severe oral and facial dyspraxia as well as grammar and vocabulary deficit (Liegeois et al., 2001)
- Another case of a child with a deletion of *FOXP2* presented with autism as well as oral facial dyspraxia (Lennon et al,2007)
- Examined 22 patients, 13 with dyspraxia: Found 5 had paternal deletions of *FOXP2* regions, 7 had maternal uniparental disomy(Feuk et al, 2006)

MOTHER AND DAUGHTER WITH A CHROMOSOME 7 TRANSLOCATION AFFECTING FOXP2

(SHRIBERG ET AL., 2006; TOMBLIN ET AL., 2009)

- Both diagnosed as having apraxia of speech associated with a de nova balanced 7;13 chromosomal translocation
- Both had cognitive and language delays
- Shriberg reports on 13 speech, prosody, and voice variables that the mother and daughter have, including spastic dysarthria, apraxia of speech, and residual developmental distortion errors.
- Similar to the KE family in cognitive and language skills (in particular, grammar difficulties); vocabulary is a relative strength.

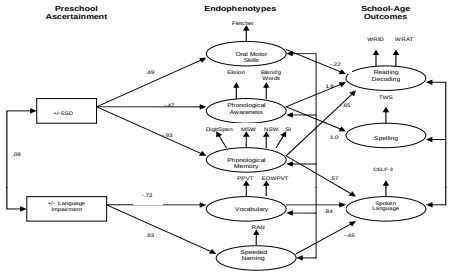
MULTIPLE DEFICIT MODEL

(PENNINGTON, 2006; MCGRATH ET AL, IN PRESS)

- Multi-factorial etiology
- Constellation of risk and protective factors determine outcomes
- Co-morbidity of disorders occurs with risk factors which are shared.
- Shared risk factors may in part be genetic
- Generalist genes have broad influences on neural processes and may account for shared risk factors
- Some candidate genes influence neural development and may impact multiple cognitive skills.
- Other genes may make a unique contribution to a single disorder.

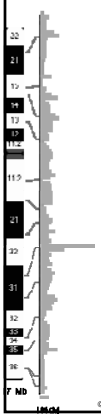
DEFINITION OF ENDOPHENOTYPES

- Objectively measurable biophysiologic, neuroanatomical, cognitive, or neuropsychological parameters that are closely associated with a behavioral trait and useful for detecting genetic influences.
- Endophenotypes are presumed to be simpler than a clinical phenotype and more directly related to genes.



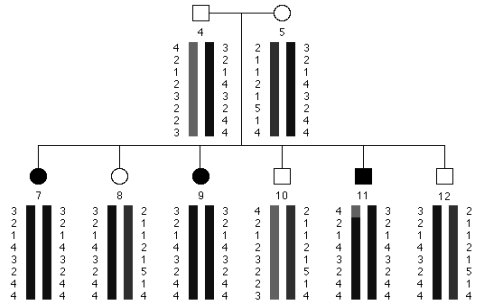
Predictions of School-age Outcomes from Early Childhood SSD and LI and their Shared Endophenotypes

Components of a Gene Mapping Study



- Collection of the sample
  - Family history
  - Clinical/phenotype information
  - DNA collection (from blood or from buccal smears)
- Genotype determination from DNA
  - Candidate genes
  - Genome Scan
- Analysis of the data - correlate genotypes and phenotypes
  - Model based linkage analysis (extended pedigrees)
  - Model free linkage analysis (sib pairs)

Linkage Analysis

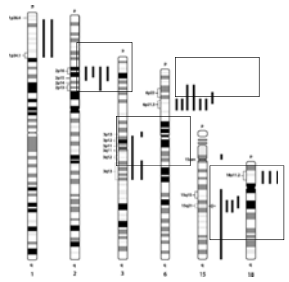


Pedigree 102

Model free linkage analysis

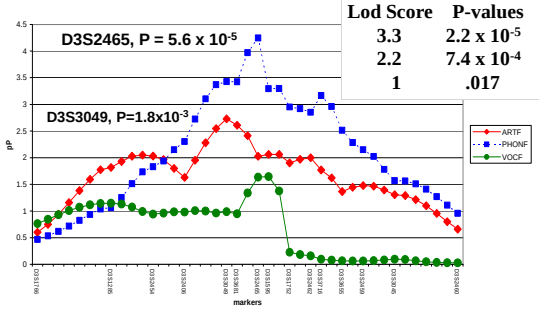
- Does not assume a specific genetic model (also called allele sharing)
- Typically a sib pair analysis (but can also be done with other types of relative pairs)
- The method evaluates allele sharing of markers (pieces of DNA that can be assayed molecularly and followed through families) at specific locations in the genome between sibs
- The statistical test in model free linkage analysis is based on excessive sharing of marker alleles among family members who are concordant for disease.
- Null Hypothesis: On average sibs will share 50% of alleles identical by descent (IBD) at an unlinked locus.

REGIONS ON CHROMOSOMES 1, 3, 6, AND 15 EXAMINED



Linkage analysis of chromosome 3

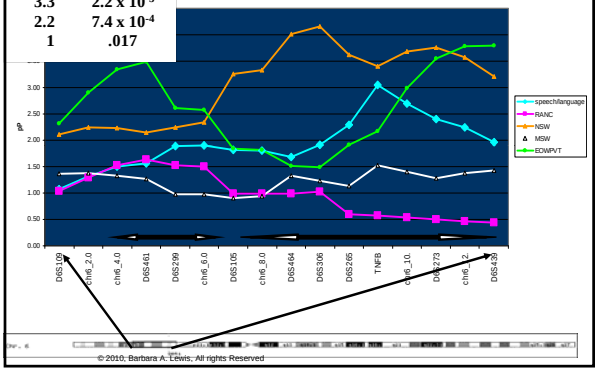
Lod Score	P-values
3.3	2.2×10^{-5}
2.2	7.4×10^{-4}
1	.017



Stein et al. Am J Hum Genet. 2004 Feb;74(2):283-97

QTL Analysis on Chromosome 6

Lod Score	P-values
3.3	2.2×10^{-5}
2.2	7.4×10^{-4}
1	.017



GENETIC FINDINGS

Genomic Region	*Traits with Linkage*
1p36	articulation, LI, SSD, SSD + LI, RD
1p33-p32	SSD, LI, vocabulary, spelling, writing, single word reading, sentence imitation
3p12-q12	Spelling, real and non-word reading, writing, articulation, sentence imitation
6p22-p21	SSD + LI, SSD, spelling, articulation
15q14	SSD, oral motor skills, reading decoding and reading comprehension, spelling
15q21	SSD, oral motor skills, reading decoding and reading comprehension, spelling
16	Non-word repetition
19	Expressive language

CANDIDATE GENES

FOXP2 7q31	Brain expressed transcription factor associated with orofacial apraxia
ROBO1 *3p12.3*	Guides axons to receptors; interferes with neuronal axon growth across the midline between brain hemispheres
KIAA0319 6p22.2	Disruption leads to impaired radial neural migration necessary for the formation of the cerebral neocortex
DCDC2 6p22.2	Modulatory; neural migration; localizes to centers for reading
DYX1C1 *(EKN1)* 15q31	Associated with reading, articulation, phonological memory

See Smith (2007) for a review of genes related to SSD, RD, LI and autism.

Parent of Origin Effects
(imprinting)

- The same trait has different phenotypic outcomes depending on if it is inherited from the mother or father.
- Imprinted genes often occur in clusters along a chromosome.
- Imprinted genes often affect cognitive and neurodevelopmental processes.
- Specific genetic syndromes may result from mutated genes that are imprints; for example, Prader-Willi and Angelman Syndrome.

COPY NUMBER VARIATION (CNV)

- Differences in the number of copies of a segment of DNA. Humans generally have two copies of each segment.
- CNVs can be deletions, duplications, inversions or translocations
- CNVs are widespread and a common phenomenon in humans- approximately 0.4% of genomes of unrelated people differ in CNV.
- CNV has been associated with developmental disorders such as autism, schizophrenia, and learning disabilities.
- CNV may account for variability in complex human behavioral traits.

EPIGENETICS

- The study of inherited changes in the phenotype by mechanisms other than DNA
- Non-genetic factors cause genes to behave differently.
- Can be transmitted through multiple generations.
- Terms such as epigenome, epigenetic code, epigenetic map parallel genetic terms.
- Epigenetic changes occur through processes such as methylation.
- Developmental disorders may be transmitted through epigenetics.
- Emphasizes that early life experiences can create lasting changes in behavior; for example, formation and maintenance of memories.

SYNDROMES AND CAS

Syndromes associated with CAS

GENETIC DISORDERS

- Caused by single gene mutations
- Categorized by mode of transmission:
  - dominant, recessive, X-linked, polygenic
- There are 2,786 abnormal genetic conditions (53% are dominant)
- Penetrance- the frequency of expression of a genotype
- Variable expressivity-genetic trait may present different degrees of severity and forms

SUMMARY OF SURVEY OF SLPS IN OHIO AND SYNDROMES

- The number of children with syndromes on SLPs' caseloads is relatively low (Mean=2.6; Range= 0-13). 33% of respondents saw no children with syndromes.
- Most common syndromes were:
  - Down's 71%
  - Fragile X 25%
  - Prader-Willi 18%
  - Williams Syndrome 11%
  - Velo-cardio-facial 10%

SURVEY RESULTS

- Most respondents rated their knowledge of syndromes as slightly above average; no one rated their knowledge as excellent.
- Most felt that some information was easy to find; however, often it was not specific to speech/language. Information was often obtained from the internet, parents of children, or health care professionals. 75% felt they could use more guidance. More common syndromes such as Down's had more information.

SOME NEURODEVELOPMENTAL DISORDERS/SYNDROMES WITH CAS

SHIRBERG, 2009

- Autism
- Chromosome translocations
- Down Syndrome (Trisomy 21)
- Fragile X Syndrome
- Galactosemia (9p13)
- Rett syndrome
- Russell-Silver Syndrome (*FOXP2)*
- Velocardiofacial Syndrome (22q11.2 del)
- Williams-Buren region microduplication (7q11.23)

CHROMOSOMAL SYNDROMES

- Deletion of parts of chromosomes
  - variable depending on part of chromosome and extent deleted.
  - 4p- or Wolf-Hirschhorn syndrome
  - 5p- or cri du chat syndrome
- Contiguous gene syndromes
  - submicroscopic section of a chromosome is missing; more discovered as genome is mapped.
  - Velocardial Facial Syndrome 22q11.2

CHROMOSOMAL SYNDROMES

- Deletion of whole chromosomes
  - Turner Syndrome 45X
  - monosomy is rare; often results in abortion
- Addition of extra whole chromosomes
  - Down's Syndrome or Trisomy 21; Trisomy of 8,9,13.
  - Full trisomies are rare; most are mosaics

TYPES OF GENETIC ABNORMALITIES

- Errors in chromosome number
  - monosomy- deletion of an entire chromosome usually due to nondisjunction
  - trisomy - an entire extra chromosome also due to nondisjunction (Example Trisomy 21)
  - polyploidy - presence of an entire extra set of chromosomes

OTHER GENETIC ABNORMALITIES

- Dicentric chromosomes - have 2 centromeres because they are made up of two broken segments of other chromosomes
- Inversions- interstitial break and segment reattaches opposite its original alignment
- Ring chromosome- two breaks in chromosome and ends join to form ring

MOSAICISM

- Chromosome rearrangement does not appear in every cell because the non-disjunction occurred near the end stage of cell division.
- Mosaic individuals may be less severe than individuals with all cells affected.

ANGELMAN VS. PRADER-WILLI

- Del of 15q11-q13
- Mother's segment of chromosome missing
- severe-profound mental retardation
- no speech or language development

- Del of 15q11-13
- Father's segment of chromosome missing
- IQ=70
- Speech/language delays
- CAS in some individuals

PRADER-WILLI SYNDROME

- Results from one of three abnormalities of chromosome 15 in a region known as the PWS/AS (15q11-q13)
  - deletion of the paternally contributed chromosome 15 PWS/AS region (70%)
  - maternal uniparental disomy (UPD) for chromosome 15 (25%)
  - translocation or other structural abnormality of PWS/AS region (5%)

PRADER-WILLI SYNDROME

- Males and females are equally affected
- Incidence is 1: 10,000
- Hyperphagia and food seeking, leading to obesity
- Neonatal and infantile hypotonia
- Feeding problems in infancy
- Developmental delay
- Average IQ is near 70

COGNITIVE PROFILE OF PWS

- Weaknesses
  - Poor auditory short-term memory
  - Pragmatic language skills
  - Sequencing abilities
- Strengths
  - Perceptual-spatial organization
  - Visuo-motor integration
  - Attention to visual detail
  - Reading decoding

SPEECH AND LANGUAGE CHARACTERISTICS OF PWS

LEWIS , FREEBAIRN, HEEGER, & CASSIDY (2002)

- Poor speech sound development
- Reduced oral motor skills
- Abnormal pitch
- Hypernasality
- Receptive/expressive language delays
- Poor pragmatic skills
- CAS in a subgroup

CAS IN GALACTOSEMIA

(SHRIBERG ET AL., IN PRESS)

- Rare genetic disorder due to gene on short arm of chromosome 9
- Results in inability to break down sugar in milk (lactose)
- Phenotype includes:
  - Cognitive impairment (50%)
  - SSD (50-60%)
  - Language impairment (90%)
  - Motor impairments (20%)
- 33 children with galactosemia and SSD ages 4-16yrs
  - 8 of 33 met criteria for CAS
  - Individuals with galactosemia had 180-fold increased risk for CAS

FUNCTIONAL IMAGING STUDIES

Pilot Data

FUNCTIONAL IMAGING STUDY OF SUBJECTS WITH SSD

LEWIS ET AL. (2008); TKACH ET AL. (IN PRESS)

- Participants: 9 Controls and 6 individuals with Speech Sound Disorders, all right-handed (age and gender matched).
- 4 Tasks: Repetition of Easy Real Words, Easy Non-word, Multisyllabic Nonsense Word, or Multisyllabic Real Word, each in separate runs
- Why "non-word" repetition? Closely matches phonological component of word learning.
- Using HUSH (Hemodynamics Unrelated to Scanner Hardware) paradigm originally developed for studies involving hearing-impaired pediatric subjects to reduce the impact of gradient noise. (*VJ. Schmithorst, MRM (51):399,2004*)

NON-WORD REPETITION TASK

- Related to phonological short-term memory , phonological encoding, phonological perception and representation
- Gives participant minimal time to process phonological information
  - Cannot draw on previous experience
  - Unrelated to IQ
  - Unaffected by social class or ethnic background
  - Highly heritable
  - Sensitive to residual problems
  - Associated with SLI, SSD, and autism

DIFFERENCES AMONG NON-WORD TASKS (SEE META-ANALYSIS BY GRAF-ESTES, EVANS, & ELSE-QUEST, 2007)

- Word-likedness- after age 5, vocabulary may aid in non-word repetition
- Number of syllables
- Articulatory complexity
- Number of items on task
- Methods of scoring
- Developmental differences

NON-WORD REPETITION MIGHT BE INFLUENCED BY:

- Hearing
- Phonological encoding
- Ability to perceive speech distinctions
- Phonological representations (robustness, precision, organization)
- Motor planning
- Articulation Skills
- Phonological Storage

EXAMPLES OF NON-WORDS

- Tayvock
- Zirdent
- Shoodep
- Diller
- Pennish
- Chovag
- Gobush

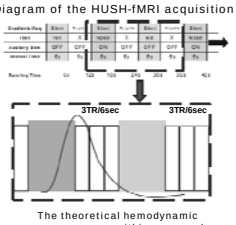
METHODS : HUSH

❖**HUSH:** Clustered volume fMRI collection paradigm referred to as HUSH (Hemodynamics Unrelated to Sounds from Hardware) , originally developed for studies involving hearing-impaired pediatric subjects to reduce the impact of gradient noise [1].

[1] *Schmithorst,VJ, et al (2004), MRM ,51, p399.*

Due to the symmetrical timing between the baseline and repetition conditions intervals, any change in MRI signal due to brain activity associated with the gradient noise is identical during both intervals and will cancel out in the post processing.

Diagram of the HUSH-fMRI acquisition

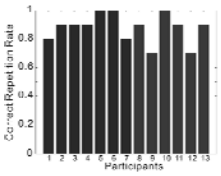


The theoretical hemodynamic response curve within one epoch

Well suited for overt repetition task:

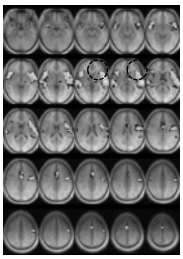
❖Eliminate gradient noise interference with auditory stimulus
❖Subject spoken response in natural speaking environment
❖Circumvent motion-related artifact
❖Subject clearly hears spoken response - on line control
❖Investigators clearly hear response

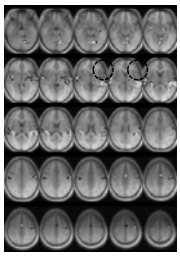
RESULTS: NWRT PERFORMANCE



NWRT performance in terms of correct repetition rate of the stimulus non-words for all participants from both the control (participants 1-7, Blue) and SSD (participants 6-13, Red) groups. The *Wilcoxon* rank sum test found no performance difference between groups at the 5% significant level (p=0.48). This suggests that the discrepancy in the brain activation patterns obtained for the SSD and control cohorts reflects an inherent difference in the functional network supporting speech production in these two groups, rather than simply being due to a difference in performance.

COMPARISON OF CONTROL GROUP AND SSD GROUP ON EASY NON-WORD REPETITION TASK



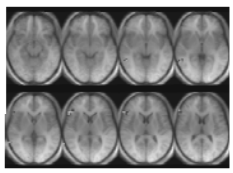


Controls (Left; N=9) SSDs (Right; N= 6)

Significant Difference in Broca's Area (circles)

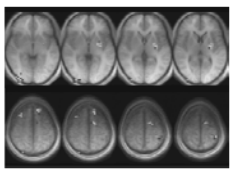
RESULTS: GROUP DIFFERENCE

Control > SSD



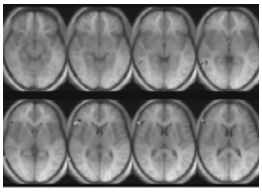
- **Exclusively right-sided**

SSD > Control



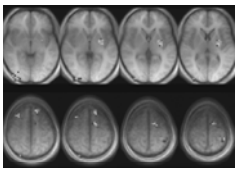
- **Bilateral and more diffuse**
- **Increased effort and/or compensatory strategy**

CONTROL > SSD



- **Exclusively right-sided**
- **Right IFG (BA45/46)**
  - Auditory feedback control of speech, vocabulary size,verbal working memory.
- **Right MTG (BA21/22)**
  - Speech perception

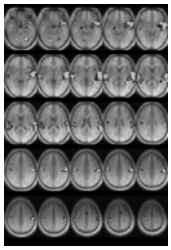
SSD > CONTROL



- **Bilateral and more diffuse**
- **Increased effort and/or compensatory strategy**
- **Bilateral SMA and PMC(BA 6)**
- **Left Post Central Gyrus (Somatosensory, BA 2) and Left Parietal Cortex (BA40)**
- **Bilateral occipital cortex (BA18 and BA19)**
- **Bilateral superior cerebellum**
- **Left Putamen**

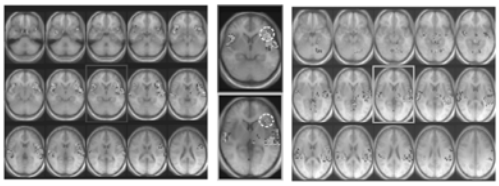
INDIVIDUAL SUBJECT ANALYSIS OF FMRI DATA

- Individual results make more sense as opposed to group analysis due to the large heterogeneity & small group size for the patient group.
- Targeted analysis was performed for each individual in ROIs related to Speech Perception & Production mainly based on the DIVA model proposed by FH Guenther.



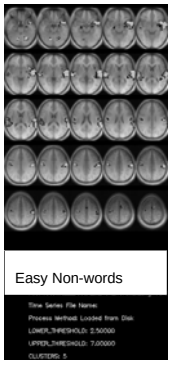
Brain Activation Pattern of ID=CAS1 (diagnosed as an Apraxia Patient) when repeating Easy Non-words.

COMPARISON OF CONTROLS TO INDIVIDUAL WITH CAS



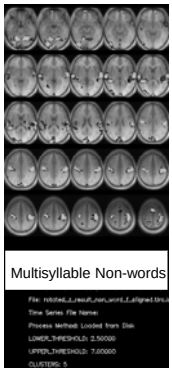
The activation pattern for an individual SSD participant with a history of CAS (Right; yellow box) during the repetition of a non-word fMRI task. The random effect result of the control group is shown on the left (red box) . Yellow circle indicates Broca's area. (Image Right=Brain Left)

SUBJECT WITH CAS: PERFORMANCE ON EASY NON-WORDS AND MULTISYLLABIC NON-WORDS



Easy Non-words

ENW (L), NW (R)



Multisyllable Non-words

ACTIVATION SUMMARY

	Brodmann Area	Control	CAS	SSD	SSD	SSD	SSD	SSD
		L	1	1	2	3	4	5
Somatosensory	**BA1** (somatosensory cortex for speech articulators)		X	R<L		R<L	L	X
	BA2 (same as BA1)	X	L	R<L	X	R<L	R=L	X
	BA3 (same as1 BA1)	R<L	R<L	R<L	X	R<L	R<L	R<L
Motor Execution	**BA4** (primary motor cortex)	R<L	R=L	R<L	X	R<L	R>L	R=L
	BA6 (initiation and sequential planning of speech movements; planning of speech utterances at articulatory and acoustic level)	R<L	R>L	R>L	X	R<L	R<L	R<L
Auditory processing (Wernicke's)	**BA22** (phonological processing for speech perception and production; phoneme processing; Perception/retrieval of single words)	R<L	R<L	R<L	R<L	R<L	R<L	R=L

. NEUROIMAGING VS. BEHAVIORAL

Participant	Genetic	Neuro	Behavioral Deficits
CAS 1	Robo 1 gene	Bilateral activation of primary motor cortex; little or no activation in Broca's	Severe apraxic; deficits in all areas- speech, language, reading, spelling
SSD 1	-	More R hemisphere activation in motor execution. R activation in Broca's and insula, indicating difficulty with articulatory planning.	Speech, language, reading, spelling; most difficulty with non-words even as adolescent.
SSD 2	-	Underactivation; expected L dominance	Speech only; Language WNL. PIQ=130
SSD 3		Reduced Broca's with R hemisphere activation; Bilateral processing of syllable and complex tones.	Speech and language but NOT reading; oral motor deficits. Spelling problems and processing speed reduced.
SSD 4	-	Bilateral processing for somatosensory and motor	Speech, language, reading and spelling problems; oral motor difficulties.
SSD 5	Linkages to chromosomes 1,3,6,7,15	Underactivation; R hemisphere processing for auditory, motor, and articulatory planning	Speech, language, reading, and spelling problems; speed of processing difficulties

MAIN FINDINGS FROM THE ANALYSIS OF INDIVIDUALS:

- Activation patterns differ in critical speech and language areas for subjects with SSD versus controls.
- Subjects with SSD differ in their activation patterns with 4 participants under-activating critical areas and 2 over-activating.
- Control subjects show the expected greater activation in the L hemisphere than in the R hemisphere during speech production.
- Subjects with SSD show more equal activation of the R and L hemispheres or, as in the case of SSD 6, greater R hemisphere activation.
- Broca's area shows the most abnormal activation patterns with 2 subjects showing little or no activation, 1 subject showing R hemisphere activation, 1 showing only partial activation, and 1 showing a normal activation pattern.

FINDINGS FOR INDIVIDUALS WITH GENETIC DIFFERENCES

Participant	Genetic	Neurological Findings	Behavioral Findings
CAS 1	Abnormal ROBO1 gene on Chromsosome 3;	Bilateral activation of primary motor cortex; little or no activation in Broca's area	Diagnosed as severe apraxia; deficits in all areas speech, language, reading and spelling.
CAS 5	Linkages to chromosomes 1,3,6,15	Underactivation; R hemisphere processing for auditory, motor, and articulatory planning	Speech, language, reading and spelling problems; speed of processing difficulties.

CONCLUSIONS

- Examining behavioral, acoustic, genetic and neuro-imaging data allows us to test hypotheses concerning the core deficits in CAS and other SSD.
- To date, genetic studies have identified candidate genes that influence neural development. These genes have broad effects on multiple cognitive processes that present with varied clinical manifestations.
- Functional neuroimaging studies suggest that while normal individuals process speech tasks in a similar manner, the processing of the same tasks by individuals with disorders is highly variable.
- Future directions include collecting a younger, more homogeneous sample with CAS, administering the complete MSAP, conducting a full genome scan, and revising our fMRI protocol to include a listening task.

METHODOLOGICAL CONSIDERATIONS

- Age of participants- possible compensatory mechanisms
- Speed of processing differences- slower processing in SSD participants may have resulted in capturing different activation
- Did not include a listen-only condition to allow us to distinguish auditory processing from speech production
- Small heterogeneous sample

SUMMARY AND CONCLUSIONS

- Understanding the genetics of CAS and other SSD has just begun. It is likely that many genes for CAS will be identified.
- Some genes will be specific to CAS and others will be generalist genes that result in co-morbid disorders.
- A Multiple Deficit Model best explains CAS and other SSD with a combination of risk and protective factors determining the disorders' expression.
- Genetic methodology and technology is developing rapidly and allowing us to study more regions of the genome faster and less expensively.
- Long-term goals are to understand the gene's expression in the brain and the effect on the resultant speech and language behaviors.

Collaborating Laboratories

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- ***University of Cincinnati***
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  SUNY Buffalo
  Lara Miscamarra, Ph.D.

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Conference Schedule

Monday: ***Childhood Apraxia of Speech: An Overview and Assessment Considerations*** **- Rebecca McCauley, Ph.D., CCC-SLP**

Tuesday: ***Medical Management of Children with Childhood Apraxia of Speech*** **- Amy Newmeyer, M.D.**

Wednesday: ***Principles for Childhood Apraxia of Speech Across Childhood*** **– Shelley L. Velleman, Ph.D., CCC-SLP**

Thursday: ***Genetic and Neurological Correlates of Childhood Apraxia of Speech*** **– Barbara A. Lewis, Ph.D., CCC-SLP**

Friday: ***Current Issues in CAS: Round-Table Discussion*** **– Rebecca McCauley, Ph.D., CCC-SLP, Amy Newmeyer, M.D., Shelley Velleman, Ph.D., CCC-SLP, Barbara Lewis, Ph.D., CCC-SLP**


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