Genetic and Neuroimaging Research in Childhood Apraxia of Speech

Barbara Lewis, Ph.D
Department of Communication Sciences
Case Western Reserve University
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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.
- 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

Participants were enrolled in our ongoing genetic study of SSD.

- 6 individuals with SSD followed longitudinally from early childhood (4-7 yrs) to adolescence.

Upon enrollment in the study at early childhood participants met the following criteria:

- Normal hearing, nonverbal IQ, and oral structures
- Deficits of speech-sounds in single words < 10th percentile of the GFTA and a severity rating of 3-4 on the KLPA
- Speech sound errors in conversational speech
  - an intelligibility rating of <90 percent
  - at least four of ten phonological processes (error types) on the KLPA
  - failure to produce at least two of ten distinctive speech-sound features

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Longitudinal Behavioral Data

Early Childhood, School Age, Adolescence

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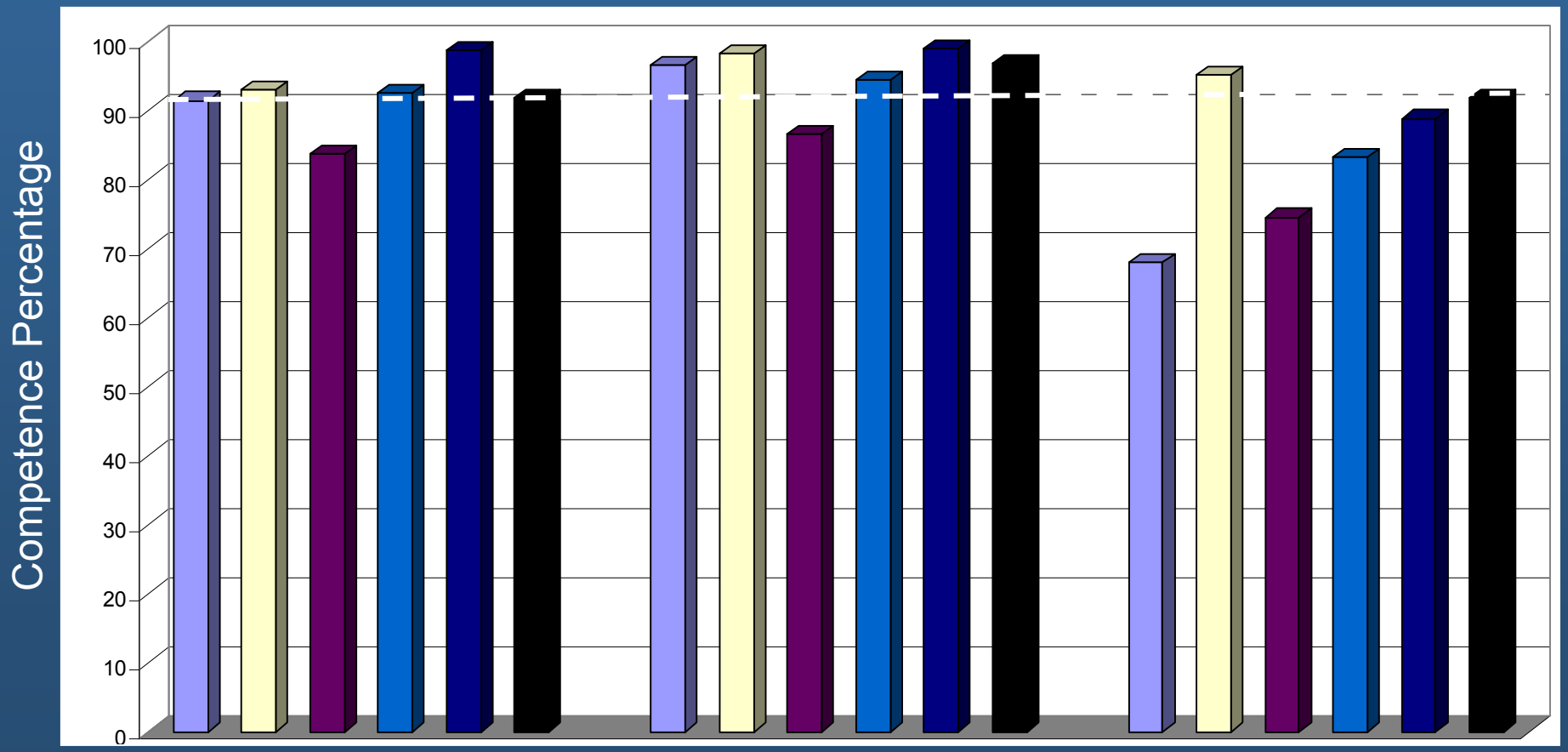
	Early childhood (4-7 yrs)	*Middle childhood (8-12 yrs)*	*Adolescence/Adult (13+)*
Speech-sound Production	GFTA-2	GFTA-2,	GFTA-2,
	PCCR	PCCR	Speech Sample
Phonological Encoding	MSW NSW	MSW NSW	MSW NSW
Language	CELF-P PPVT	CELF-4 PPVT	CELF-4 PPVT
Reading			
Decoding		WRMT-R	WRMT-R
Comprehension		WIAT-2	WIAT-2
Spelling		TWS-4	TWS-4
Oral-Motor	TFS (Robbins & Klee)	Fletcher Time-by-Count	Fletcher Time-by-Count
Phonological Memory	Sentence Imitation	Sentence Imitation	Sentence Imitation
Phoneme Awareness	CTOPP	CTOPP	CTOPP
Speed of processing	RAN colors	Perceptual Speed Finding As RAN colors	Perceptual Speed Finding As RAN colors

Competence Findings



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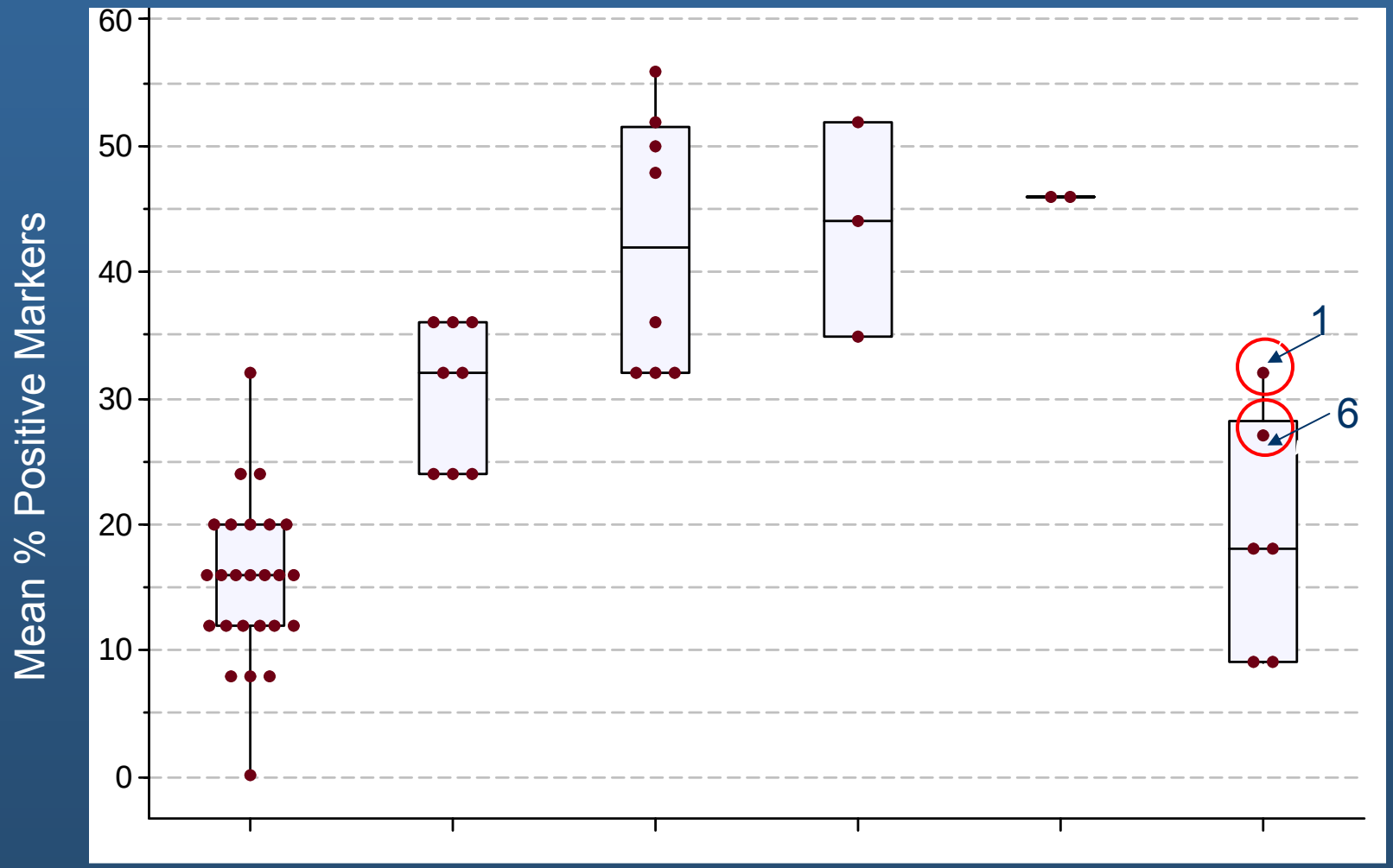
% Positive Diagnostic Marker Findings



Speech Delay | *GALT* Controls | *GALT* CAS | Chr 4q;16q | *FOXP2* | SSD

Control Groups | Target Groups

Study Samples

Tier	Domain	Promising Markers					
			A	1	6		
		Precision				Stability	
Segmental	Vowels/ Diphthongs	- Reduced Space - Lengthened Durations - Reduced Pairwise Duration Variability	√ √	√ √ √	√ √	- Unstable Space - Unstable Duration	√ √
	Consonants	- Spatiotemporal Distortions - Cluster Disruptions - Nasal Emissions	√	√	√		
	Vowels/Diphthongs & Consonants	- Increased Epenthetic Errors in Complex Contexts - Word/Syllable Segregation		√		- Unstable Phoneme Errors	
Supra-segmental	Phrasing	- Increased Repetitions and Revisions - Reduced Speech-Pause Variability Ratio	 √		√		
	Rate	- Slow Speaking Rate - Slow Articulation Rate	√ √		√	- Unstable Speaking Rate - Unstable Articulation Rate	
	Stress	- Reduced/Increased Lexical Stress - Reduced Emphatic Stress - Reduced Sentential Stress	√ √ √		 √	- Unstable Emphatic Stress - Unstable Sentential Stress	
Voice	Loudness	- Reduced/Increased Vowel-Consonant Intensity Ratios		√R			
	Pitch	- Low/High F0 - Reduced/Increased F0 Range					
	Laryngeal Quality	- Strained; break/shift/tremulous					
	Resonance Quality	- Nasal; nasopharyngeal		√N			

Red: Consistent with CAS; Green: Consistent with Dysarthria; Blue: Consistent with CAS and Dysarthria

Genetic Linkage Studies

Chromosomes 1,3,6 and 15

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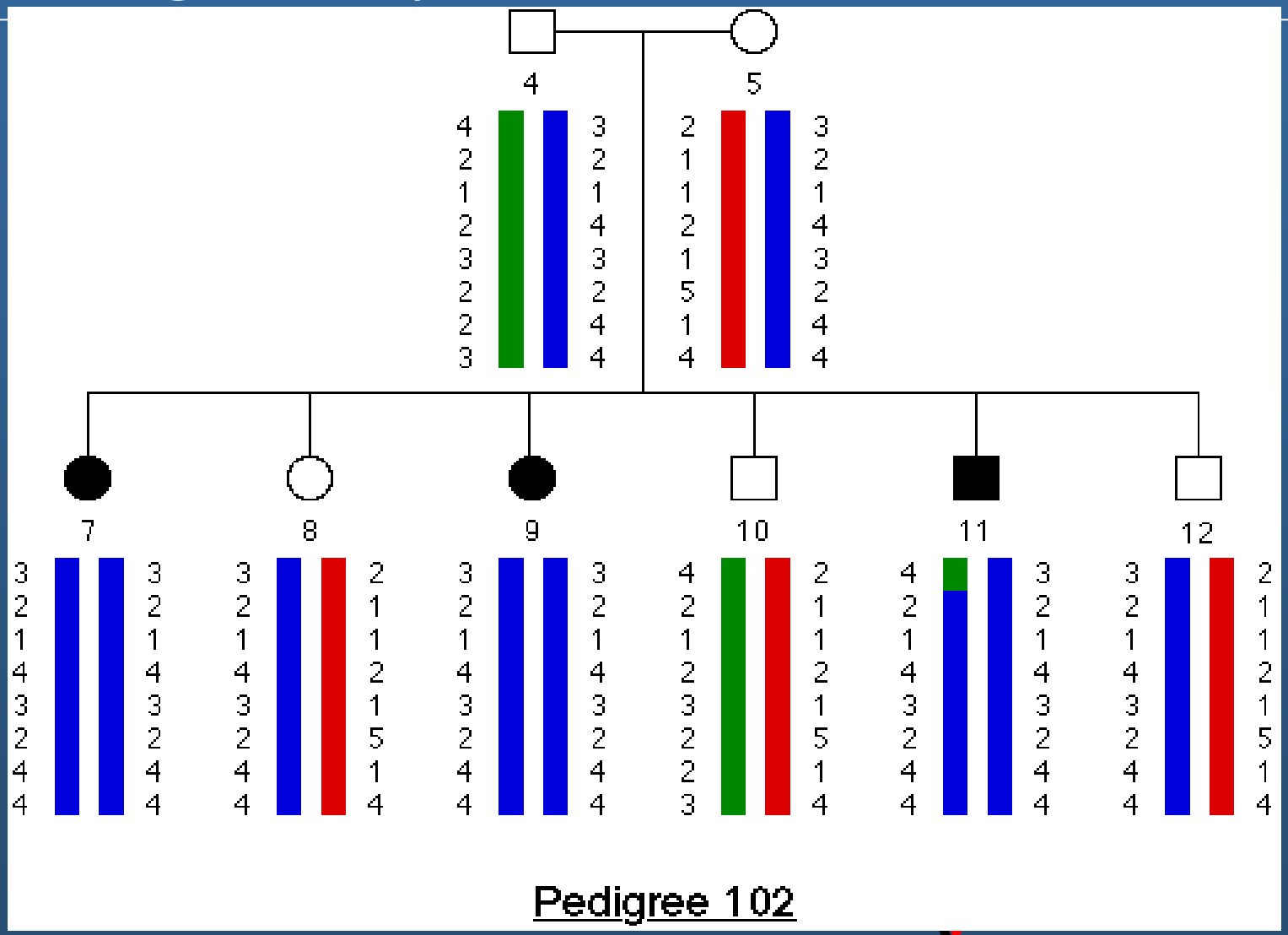
Components of a gene mapping study

- Collection of the sample
  - Family history
  - Clinical/phenotype information
  - DNA collection (from blood or saliva)
- 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)

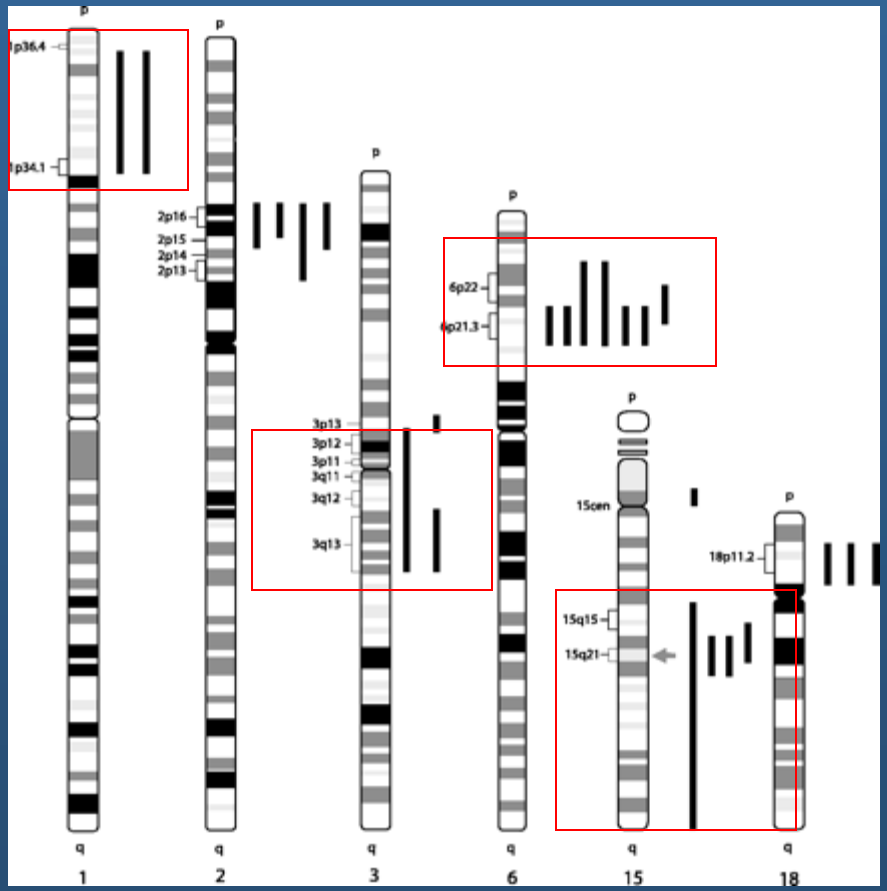
Model free linkage analysis

- 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

Linkage Analysis



Regions on chromosomes 1, 3, 6, and 15 examined



Genetic findings

Genomic Region	*Traits with Linkage*
1p36	GFTA, LI, SSD, SSD + LI
1p33-p32	PPVT, SSD, LI, TWS, TOWL, Word ID, Sentence Imitation
3p12-q12	TWS, Word ID, Word Attack, NSW, MSW, articulation factor score, Sentence Imitation, TOWL
6p22-p21	TWS, MSW, NSW, SSD + LI, SSD
15q14	SSD, oral motor skills, Word Attack, Word ID, Listening comp., TWS
15q21	SSD, oral motor skills, Word Attack, Word ID, Listening comp., TWS
Conclusion	Two of the 6 participants with SSD showed linkages: ID=1 linked to chromosome 3; ID=6 linked to all chromosomes.

Functional Imaging Studies

Overt Repetition Task of Real and Nonwords

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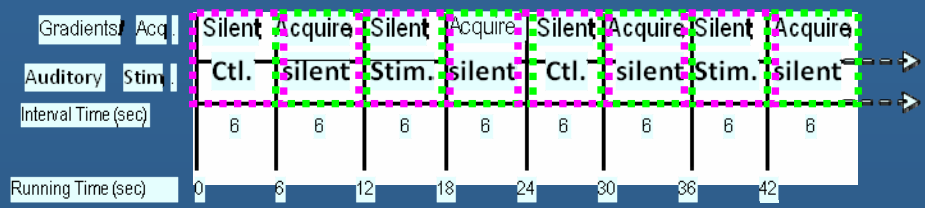
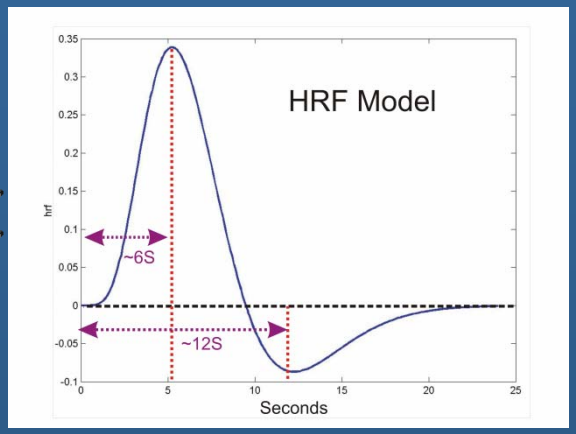
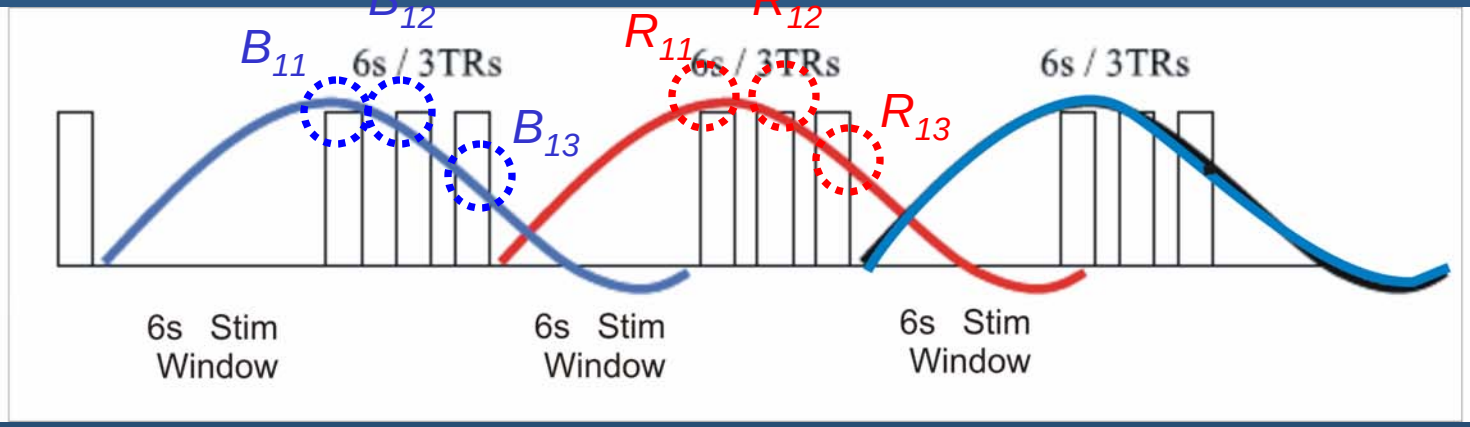
Functional Imaging Study of Subjects with SSD

- 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*)

Diagram of the HUSH Paradigm



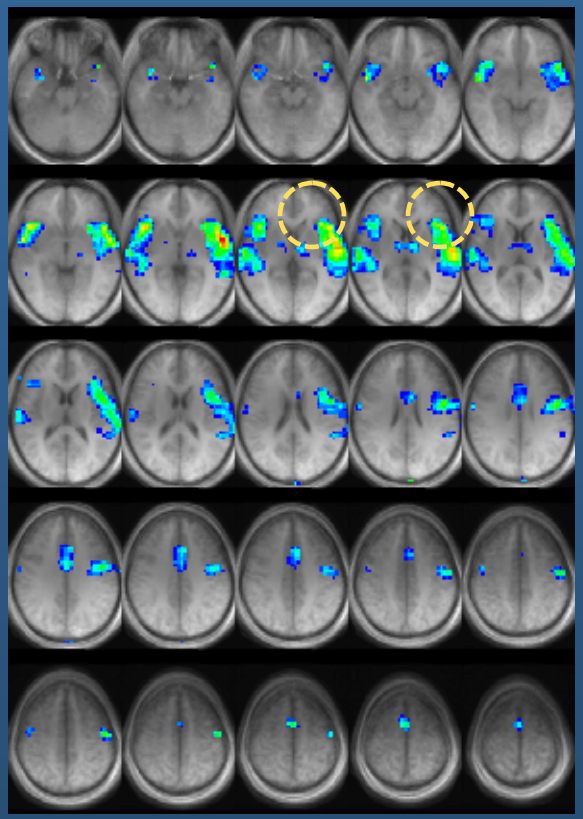


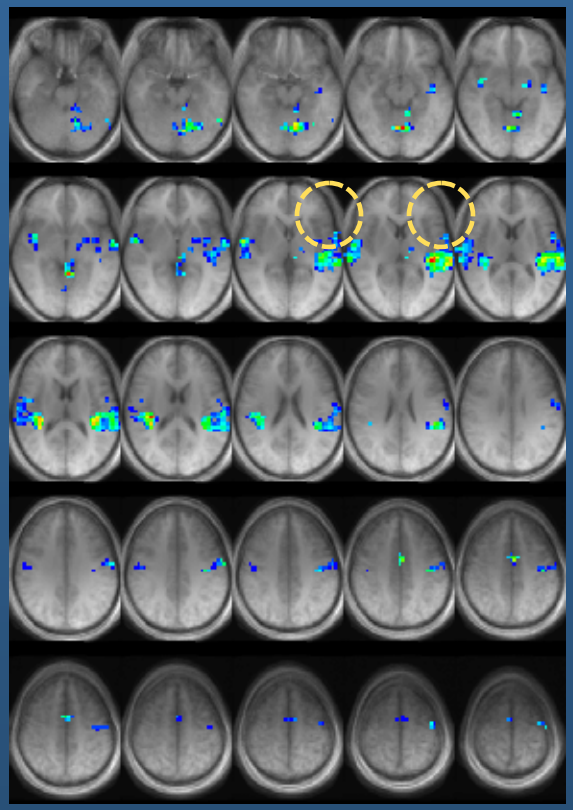


Hemodynamics Unrelated to Scanner Hardware

(Modified on the basis of NIH Grant Proposal by Drs. Lewis & Tkach)

Comparison of control group and SSD group on easy nonword repetition task

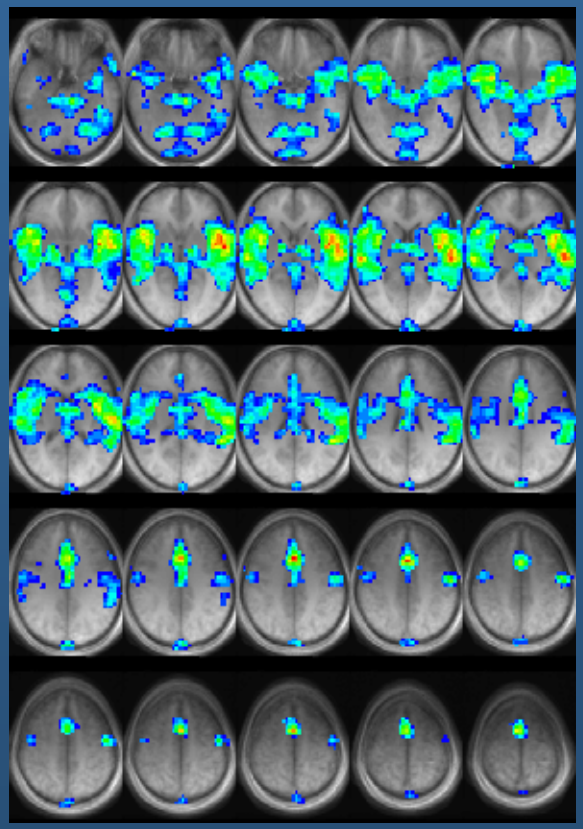


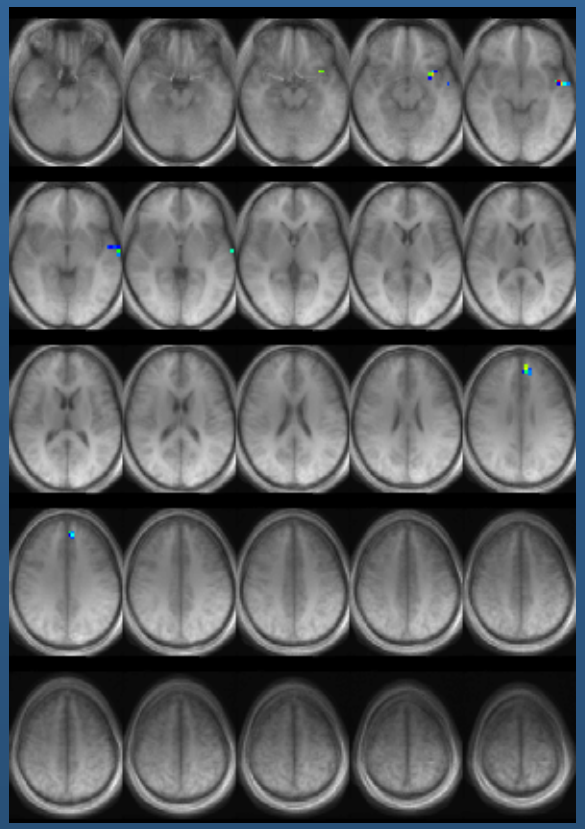


Controls (Left; N=9) SSDs (Right; N= 6)

Significant Difference in Broca's Area (yellow circles)

Group Results for Multisyllabic Nonwords

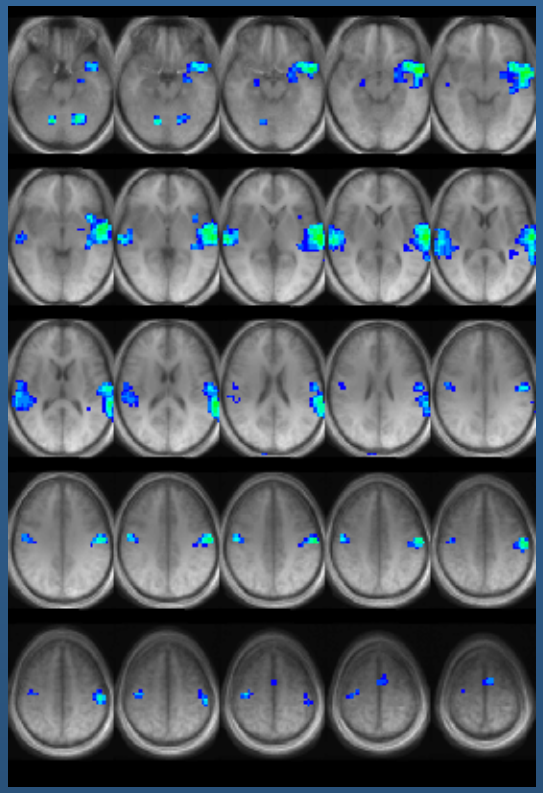




Control (Left; N=9), SSD (Right; N=6)

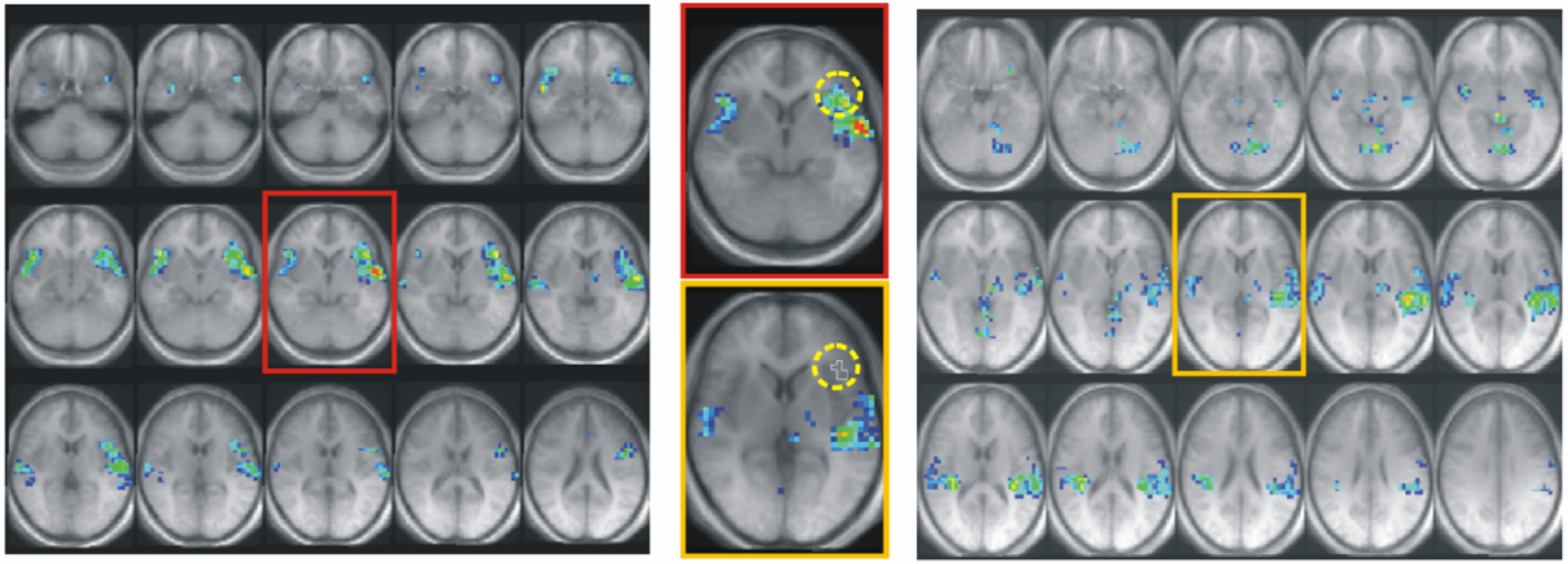
Individual subject analysis of fMRI data

- 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=1 (diagnosed as an Apraxia Patient) when repeating Easy Nonwords.

Comparison of Controls to Individual with CAS

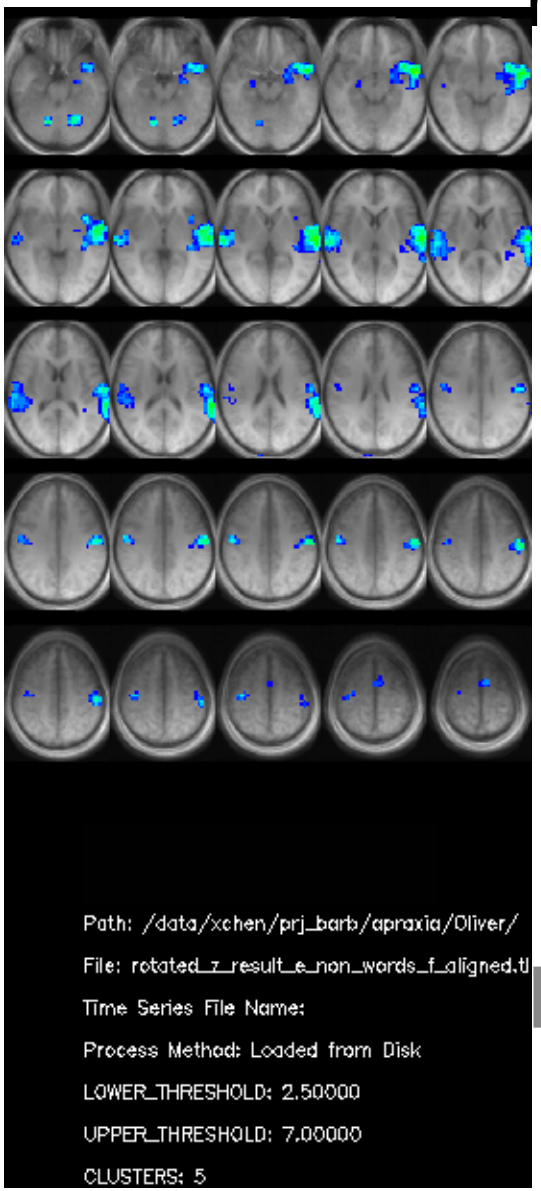


The activation pattern for an individual SSD participant with a history of CAS (Right; yellow box) during the repetition of a nonword fMRI task. The random effect result of the control group is shown on the left (red box) . Yellow circle indicates Broca's area. (Image Right=Brain Left)

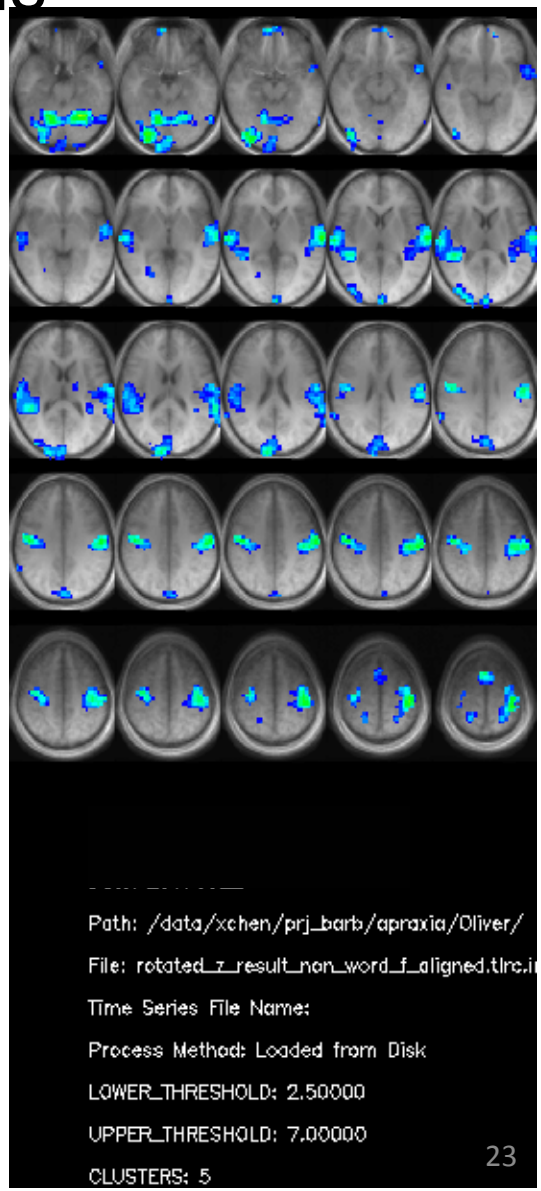
Main Findings from the analysis of individuals:

- 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.

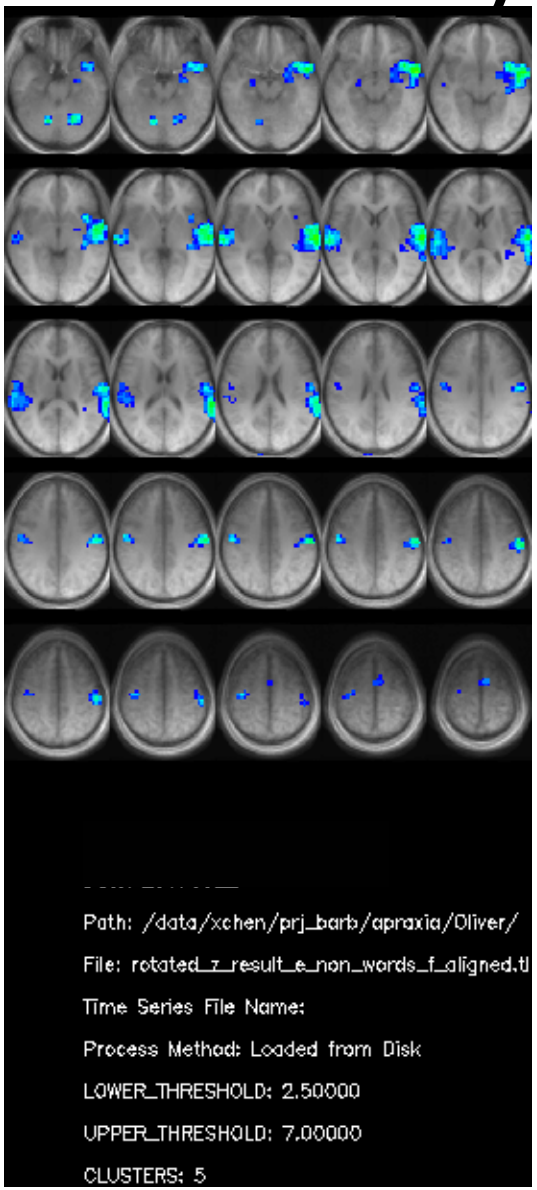
Subject 1: performance on easy nonwords and multisyllabic nonwords



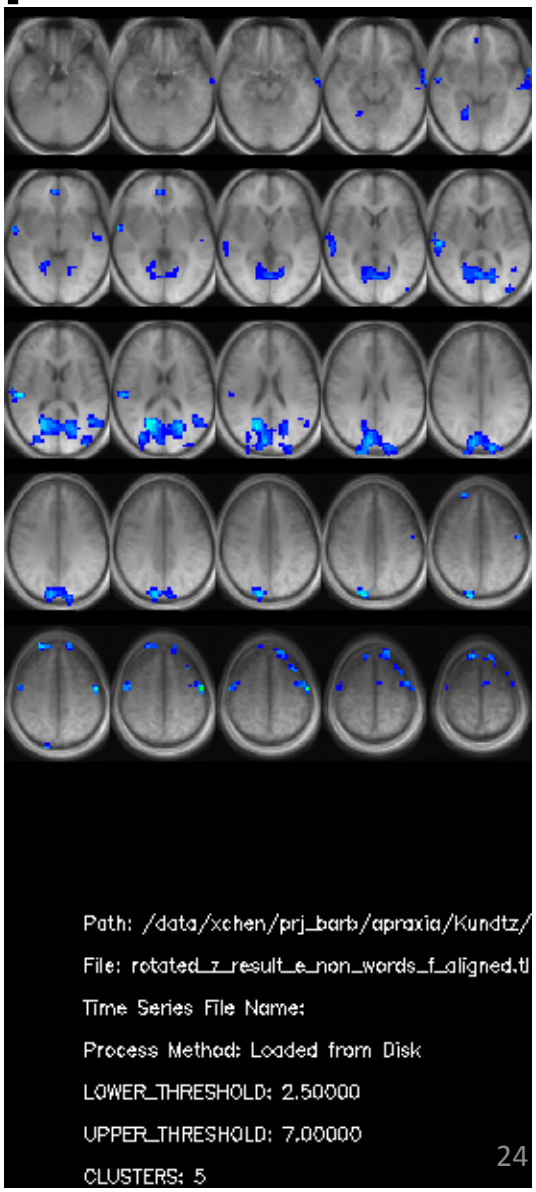
ENW (L), NW (R)



Easy Nonword Reptition



ID=1 (L), ID=6 (R)



Comparisons of participants with genetic differences to controls in activation patterns

Participant	Motor Execution Primary motor (BA 4, 6)	Auditory Processing Wernicke's (BA 22)	Auditory Information Heschl's (BA 41,42)	Language Production Broca's (BA 44, 45)
Controls	R<L (4) R<L (6)	R<L	R>L (41) R<L (42)	L only (44) R < L (45)
1	R=L (4) R>L (6)	R<L	R>L (41) R<L (42)	No significant activation
6	R=L (4) R<L (6)	R=L	R (41) R (42)	No significant activation

Findings for individuals with genetic differences

Participant	Genetic	Neurological Findings	Behavioral Findings
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.
6	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, acoustical, 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 affects 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.

Collaborating Laboratories

- ***Case Western Reserve University (Epidemiology and Biostatistics)***

  Sudha Iyengar, PhD

  Catherine Stein, Ph.D.

  Dmitry Leontiev

  Case Western Reserve University (Pediatrics)

  Gerry Taylor, Ph.D.

- ***University of Wisconsin Madison***

  Larry Shriberg, PhD

- ***University of Cincinnati***

  Scott Holland, PhD

  Vince Schmithorst, Ph.D.

- ***Case Western Reserve University (Communication Sciences)***

  Barbara Lewis, PhD

  Amy Hansen, M.A.

  Lisa Freebairn, M.A.

  Case Western Reserve University (Radiology)

  Jean Tkach, Ph.D.

  Xu Chen, Ph.D.

  SUNY Buffalo

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