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THE BIG LEAP: UNDERSTANDING STUTTERING WITHIN THE CONTEXT OF DEVELOPMENTAL NEUROSCIENCE.

3/9/2012

Outline

- Developmental cognitive neuroscience: An introduction
- Brain development in people who stutter
  - Structure (Neuroanatomy)
    - Volume
    - Thickness
    - Connectivity
  - Function (Neurophysiology)
    - MEG
    - fMRI
- Summary & Conclusions

Developmental Stuttering

- Developmental disorder affecting speech fluency

- Motor Speech characteristics:
  - frequent and involuntary repetitions and prolongations of sounds
  - silent blocks

- Non-speech characteristics
  - Cognitive affective
  - Communication impairment
  - Quality of life

- Prevalence: approx. 5% of preschool children

- Onset: between of 2 and 5 years of age
  - 85% prior to age 3.5 years
    - 65% recover within 2 years of onset

(Bloodstein & Ratner, 2008; Yairi & Ambrose, 1999)

Brain structure & function studies of developmental stuttering
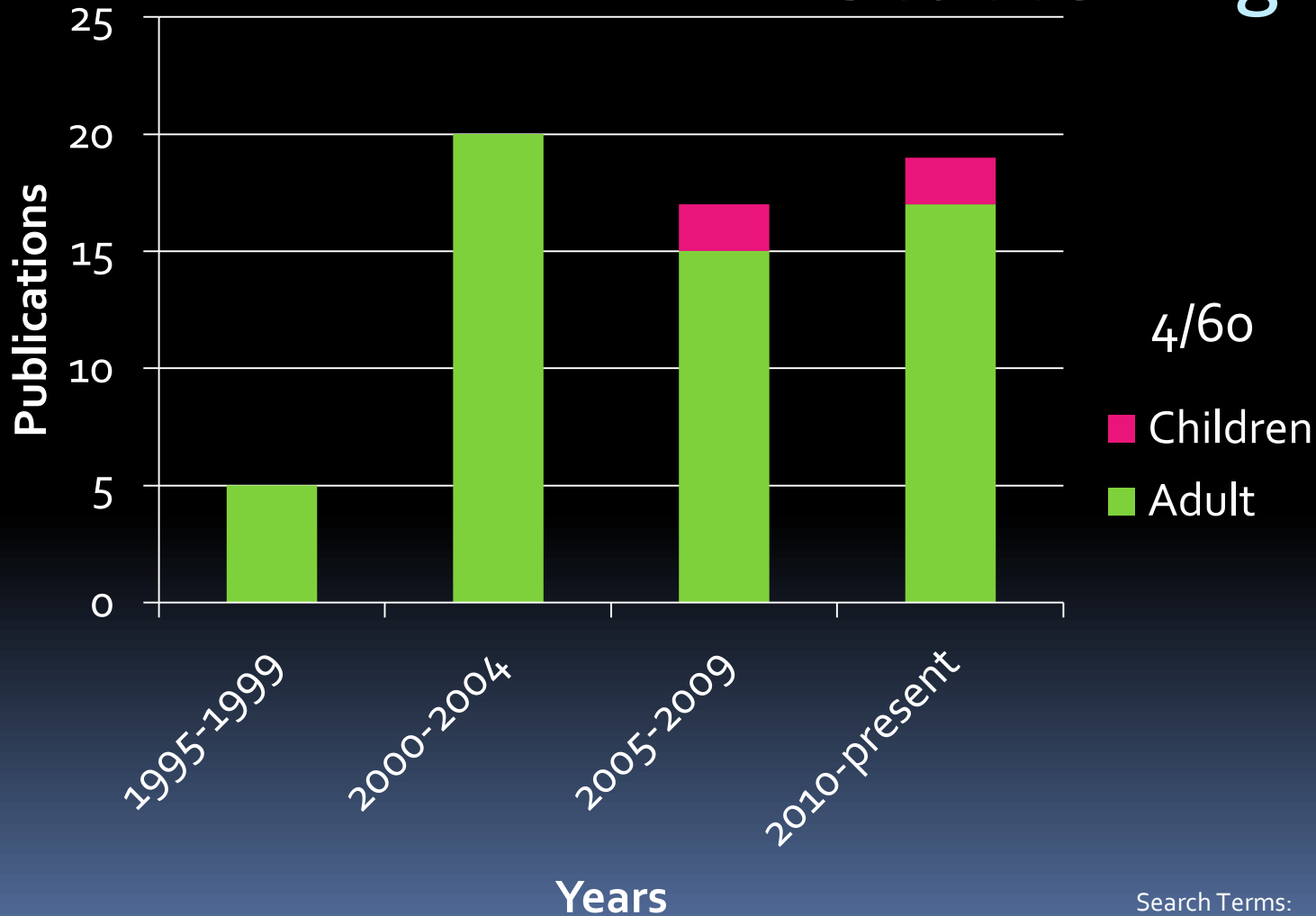
Busan et al. (2012)
Xuan et al. (2012)
Beal et al. (2011)
Chang et al. (2011)
Choo et al. (2011)
Kicuchi et al. (2011)
Loucks et al. (2011)
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Toyomura et al. (2011)
Liotti et al. (2010)
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Hampton et al. (2008)
Watkins et al. (2008)
Weber-Fox et al. (2008)
Beal et al. (2007)
Cykowski et al. (2007)
Song et al. (2007)
Brown et al. (2005)*
Biermann-Ruben et al. (2005)
Corbera et al. (2005)
Neumann et al. (2005)
Foundas et al. (2004)
Jancke et al. (2004)
Weber-Fox et al. (2004)
Blomgren et al. (2003)
DeNil et al. (2003)
Foundas et al. (2003)
Neumann et al. (2003)
Preibisch et al. (2003)
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Stager et al. (2003)
VanBorsel et al. (2003)
Viswanath et al. (2003)
Sommer et al. (2002)
DeNil et al. (2001)
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Ingham et al. (2000)
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Khedr et al. (2000)
Salmelin et al. (2000)
DeNil et al. (1998)
Salmelin et al. (1998)
Braun et al. (1997)
Fox et al. (1996)
Wu et al. (1995)
Strub et al. (1987)

Publications

25
20
15
10
5
0

1995-1999
2000-2004
2005-2009
2010-present

Years

4/60

■ Children

■ Adult

Search Terms:
EEG, MEG, MRI, fMRI, PET, fNRIS, TMS

Why the focus on adults?

- Earliest work utilized computed tomography (CT) & positron emission tomography (PET)
  - Requires exposure to radiation
- Following work moved to sMRI & fMRI
  - No tracer
  - No radiation exposure
  - Early MRI environments were not child friendly
    - Located in medical centers
    - Noisy
    - Head movement had to be kept to a minimum
    - Group analysis preparation issues (e.g., brain normalization)
- Expense

What has changed?

- sMRI & fMRI
  - Increased access to equipment & knowledge
  - Advances in:
    - Acquisition paradigms
      - E.g., sparse scanning; resting state, diffusion
    - Equipment
      - E.g., MR compatible goggles, movie screens, headphones
    - Analysis preparation
      - E.g., Paediatric templates for normalization
    - Investigator creativity!
      - E.g., "basketball game" vs "limb movement task"
    - Well established psychophysical paradigms
- Increased interest in brain development
  - Increasing access and use of EEG, MEG, fNIRS

What has stayed the same?

Developmental Cognitive Neuroscience

- An emergent field

- Convergence of human developmental and cognitive neuroscience
  - Relating changes in brain structure & function in aging to the associated behavioral changes

- Dedicated journal
  - Founded in 2011

- Expertise
  - Speech-language clinician scientists are poised to contribute

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    - Thickness
    - Connectivity
  - Function (Neurophysiology)
    - MEG
    - fMRI

Neuroanatomic Abnormalities

- Manual Morphometry
- Abnormal asymmetry of occipital lobe volume
  - Left handed male twin siblings who stutter
  - Computed tomography images
    - Correlated with PT asymmetry
      - (Strub et al., 1987)
- Abnormal asymmetry of planum temporale volume
  - 14 PWS, 14 Controls (mix of gender & handedness)
  - MRI images
  - Behavioral relation
    - (Foundas, 2004)
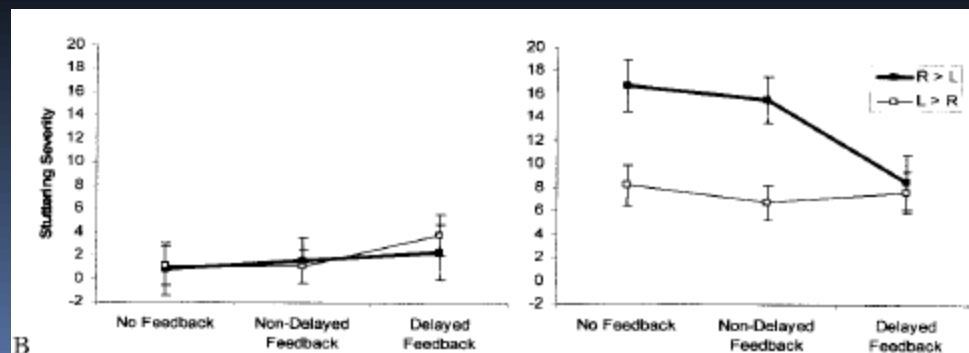
Neuroanatomic Abnormalities

- Voxel-based morphometry (VBM)
  - Automated whole brain exploration of morphological differences between groups with no required apriori hypotheses

- Increased white matter volume (WMV) underlying right hemisphere superior temporal gyrus, planum temporale, precentral gyrus and IFG
  - 10 (8M) PWS, 10 (8M) Controls; all right handed;
  - MRI images
  - No findings related to GMV
    - Jancke et al. (2004)
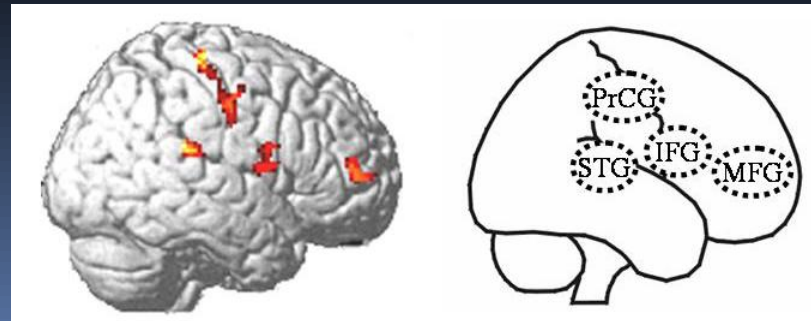
Voxel-based morphometry of auditory and speech-related cortex in stutterers

Deryk S. Beal[a], Vincent L. Gracco[c,d], Sophie J. Lafaille[a] and Luc F. De Nil[a,b]

- **Participants**
  - 26 men who stutter (x = 30.29 years, s.d.= 7.12)
    - Severity ranged from SSI-3 5 - 49
 - 28 matched controls (x = 30.53 years, s.d.= 6.44)
- **Image Acquisition**
  - 1.5-T GE Echospeed MRI system
  - 8 channel head coil
  - T1 FSPGR
- **Analysis**
  - normalised, segmented, smoothed, modulated
  - Independent 2-sample t-test; covariate = TGMV

Results
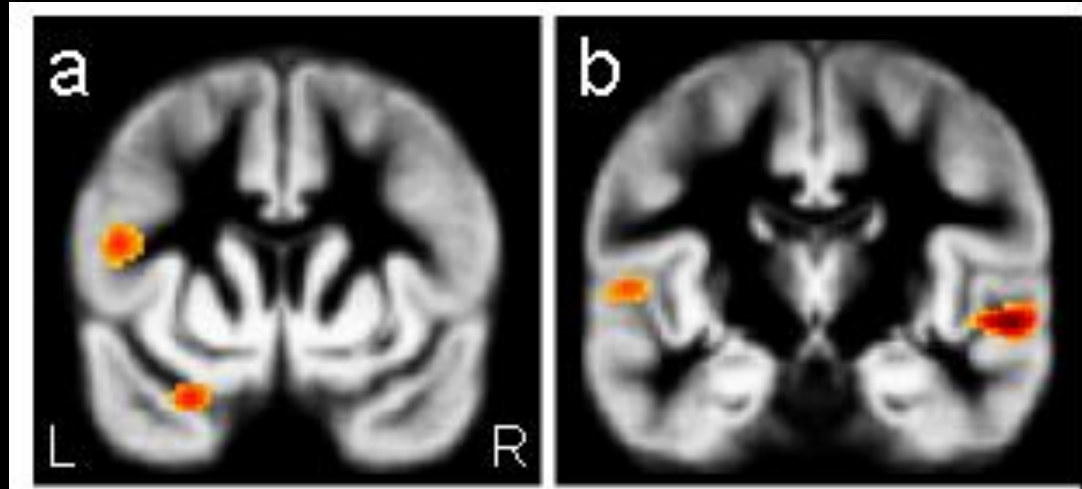
Grey Matter Volume (p<.001 uncorrected)

- Left Hemisphere:
  - Superior temporal gyrus
  - Inferior frontal gyrus
  - Insula
- Right Hemisphere:
  - Superior temporal gyrus
  - Cerebellum

Limitations

- Despite stuttering having its onset at approximately 3.5 years old the reviewed studies of morphometry investigated adults who stutter

- Unknown if morphological abnormalities are reflective of the underlying genotype or differences in maturation / compensation for stuttering

- Examining morphological differences closer to the time of onset will take us one step closer to clarifying this relation

Voxel-based morphometry in children who stutter

- Common criteria:
  - 11 Controls (*M* = 119 months; *s.d.* = 22 months) & 11 CWS (*M*= 114 months; *s.d*. = 18 months)
  - Right handed
  - English as primary language
  - Negative history of speech, language or hearing problems.
  - Speech, language and hearing screening by an s-lp

- Specific criteria for CWS
  - Onset of stuttering in childhood (pre-puberty).
  - A minimum of 3% within-word disfluencies in at least one of two speaking conditions (reading, conversation).
  - Mild, moderate or severe on the Stuttering Severity Index (Riley, 1994).

Voxel-based morphometry in children who stutter

Table 1 Means and standard deviations of participant characteristics		
	Control participants (n = 11) Mean (SD)	Children who stutter (n = 11) Mean (SD)
Age in months	119.18 (22.46)	114.18 (18.07)
GFTA-II	104.36 (2.98)	102.45 (6.15)
PPVT-III	121.45 (11.94)	118.72 (17.26)
SSI-III	0 (0)	22.09 (8.40)

Methodology

- Image Acquisition
  - 1.5-T GE Echospeed MRI system
  - 8 channel head coil
  - T1 FSPGR
- Analysis
  - normalised, segmented, smoothed, modulated
  - paediatric template – (Wilke et al., 2008)
  - Independent 2-sample t-test
    - covariate = AGE, PPVT, TGMV

Results
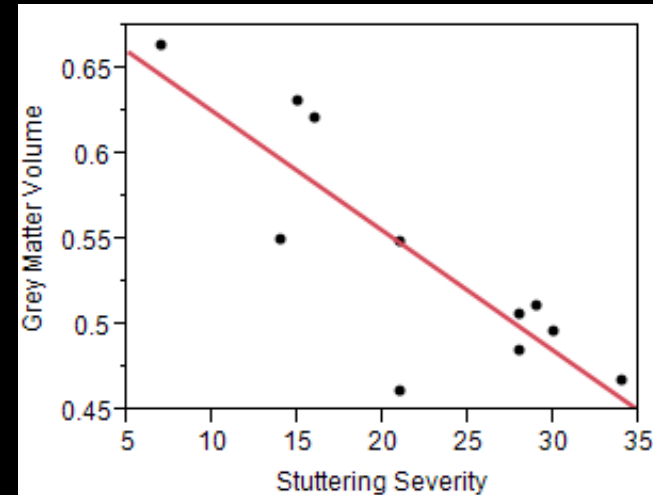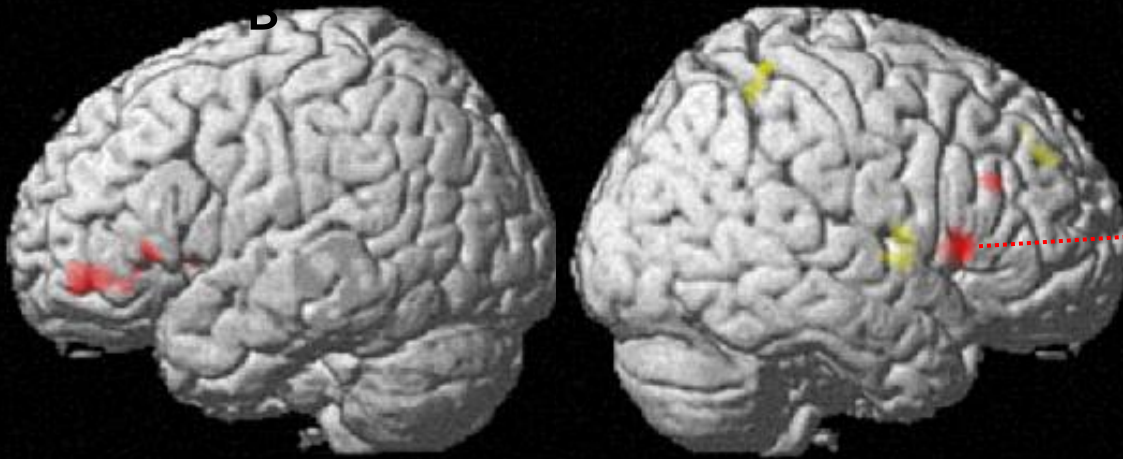
• Regions of decreased GMV in children who stutter
- Left pars triangularis
- Left pars opercularis
- Right pars opercularis

•Regions of increased GMV in children who stutter
- Right superior temporal gyrus
- Right Rolandic operculum
- Right parietal lobule
- Right post central gyrus

• Reduced GMV in bilateral inferior frontal gyrus in children who stutter also reported by Chang et al. (2008).
• Negative correlation between GMV in right inferior frontal gyrus and stuttering severity.

Beal et al. (under revision)

Implications

Frontal Gray Matter
Shape: F=3.16; p=0.024
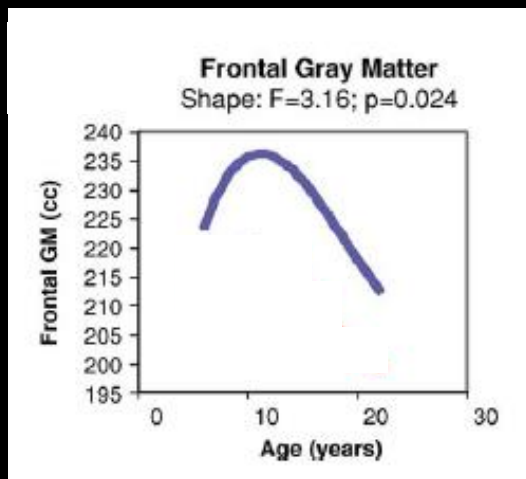
224 girls, 287 boys
Thompson et al. 2005
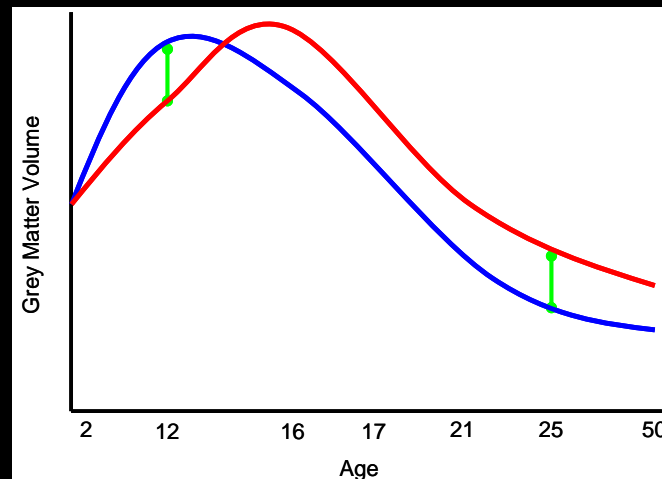
Hypothetical Curves

1. Abnormal developmental trajectory for regional grey matter volume

2. Children who stutter may have reduced neural resources for the accurate or efficient processing of speech sounds

3. Adults who stutter may continue on an abnormal trajectory of development resulting in less efficient neural organization

Grey Matter Development in PWS (Beal et al., in preparation)

- Is the trajectory of grey matter development in left inferior frontal gyrus and/or other speech network regions different in people who stutter than in people who are fluent speakers?

- Hypothesis:

  - CWS will present with grey matter thinning in pars opercularis relative to peers and AWS will present with grey matter thickening relative to peers.

Participants

- 98 participants
- Right-handed males with English as their primary language
- Normal developmental and medical history
- The 46 people who stutter ranged in age from 7 to 47 years (x = 25.66, s.d. = 8.33) and the 52 control participants from 6 to 48 (x = 27.90, s.d. = 7.60). The two groups did not differ in age (t(96) = 0.153, p = 0.88).
- People with developmental stuttering were identified by a speech-language pathologist. Stuttering severity ranged from very mild (5) to very severe (49) (x = 21.31, s.d. = 9.45) measured by the Stuttering Severity Index–3 (Riley, 1994).

Data Collection

- Data for 51 (23 people who stutter, 28 controls) participants were collected on a 1.5-T Echospeed MRI system (GE Medical Systems) at the Toronto Western Hospital.

- The data for the remaining 47 participants (23 people who stutter, 24 controls) were collected on a 1.5-T Signa Excite magnetic resonance imaging system (GE Medical Systems) at the Hospital for Sick Children in Toronto.

Cortical thickness
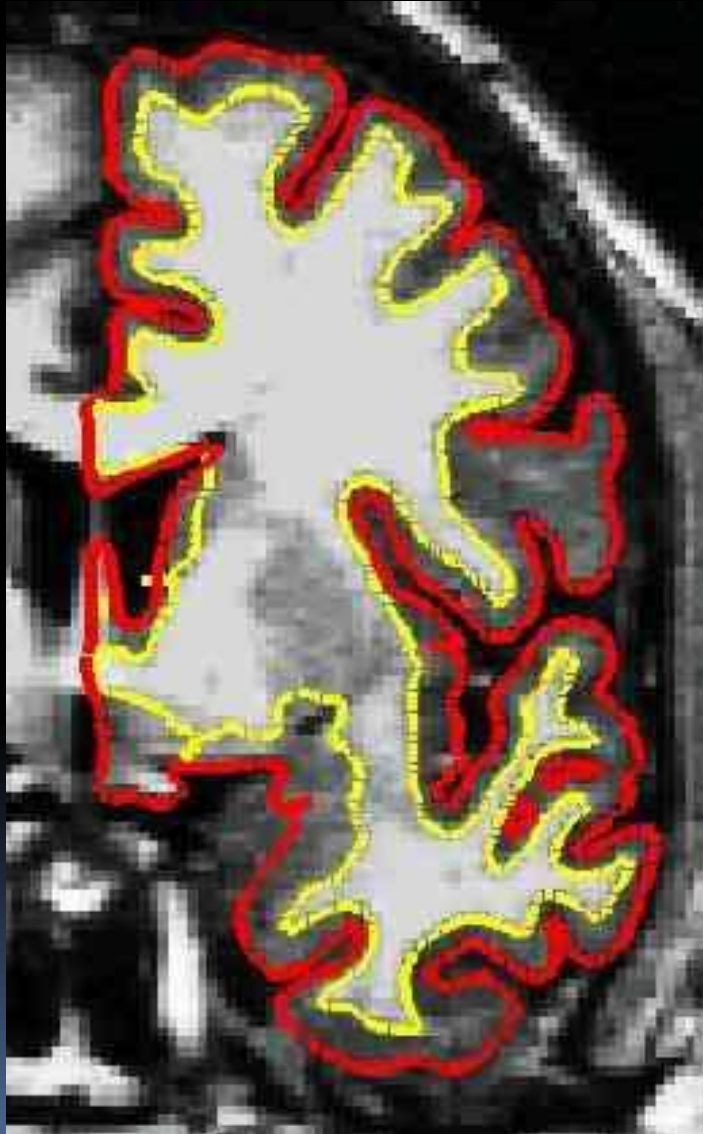
- Distance between grey and white matter boundary

- Measured at numerous points across cortex

- A real and stable measurement of grey matter development

Data Preparation
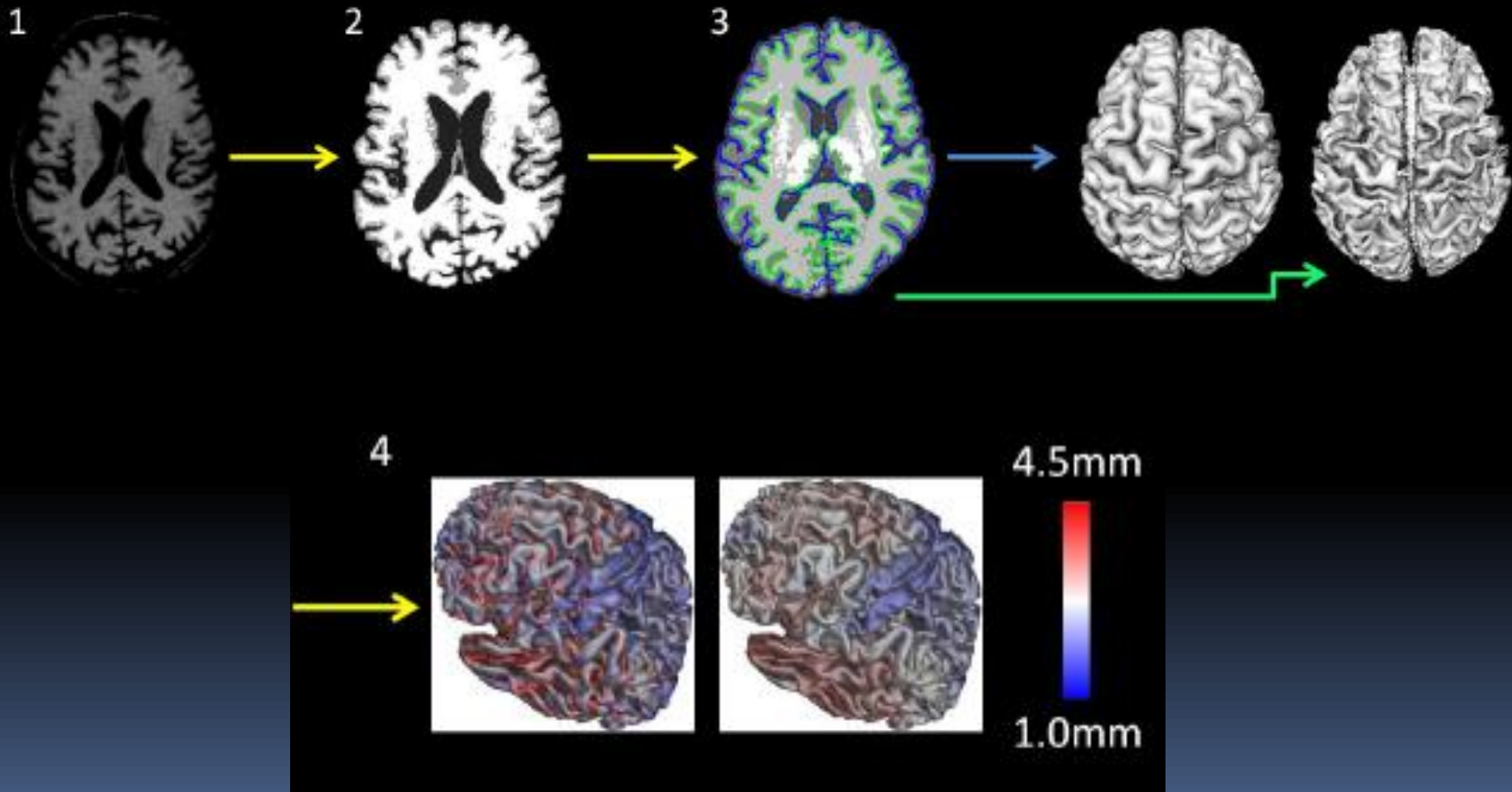
Data Analysis

- Un-normalized, native-space thickness values were used in all analyses owing to the poor correlation between cortical thickness and brain volume (Ad-Dab'bagh et al., 2005).

- Appropriate measures were taken to minimize the potential confound of data originating from 2 different sites.
  - Visual inspection
  - Scanner type included as a nuisance variable in the statistical model

Perisylvian language areas (ROI Selection)

Pars Opercularis

Motor Cortex

Primary auditory cortex / posterior STG
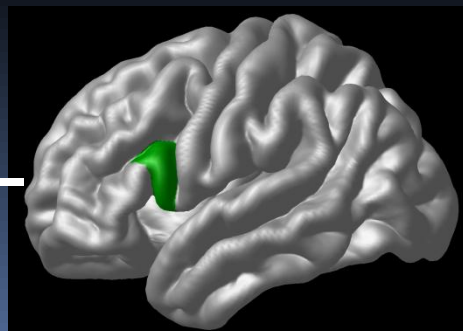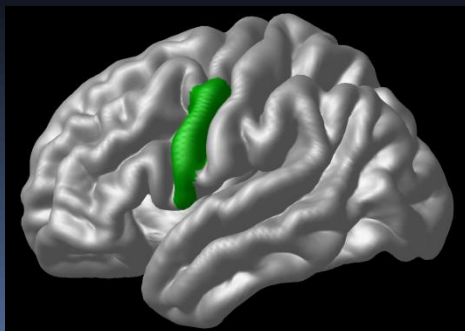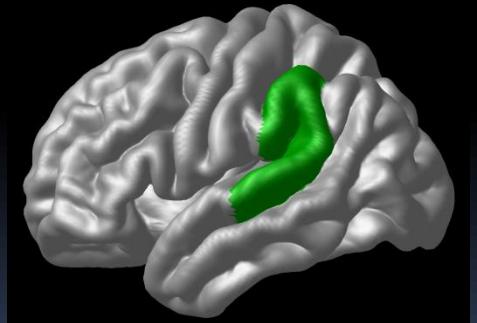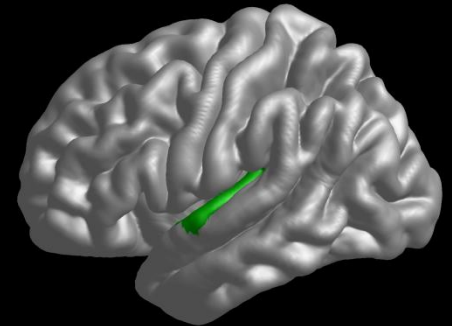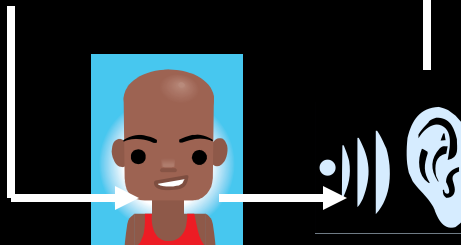
Results

- Results slides removed as data are in publication. Please email dsbeal@bu.edu for more information.

Pars Opercularis: Anatomic Characteristics
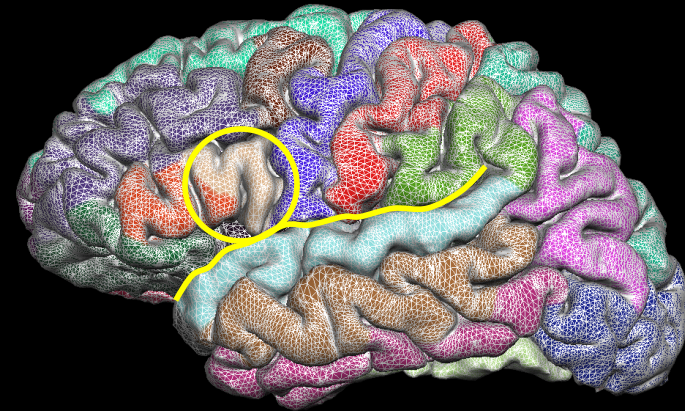
- Aka BA44 / Broca's area
- Linked to premotor cortex, posterior superior temporal gyrus and inferior parietal cortex

Frey et al., 2008; Glasser & Rilling, 2008; Petrides et al., 2005)

Pars Opercularis: Functional Characteristics

- Phoneme & syllable store
- Active during both sound perception and production
- Grapheme to phoneme mapping
- Phonetic encoding; phoneme-to-articulatory codes
- Homologous to monkey F5 (mirror neurons); role in learning
- Neural representations of speech sounds

Ghosh et al., 2004; Guenther, 1994; Guenther et al., 2006, 2010; Indefry & Levelt, 2004; McNealy et al., 2010; Newman & Tweig, 2001; Vigneau et al., 2006)
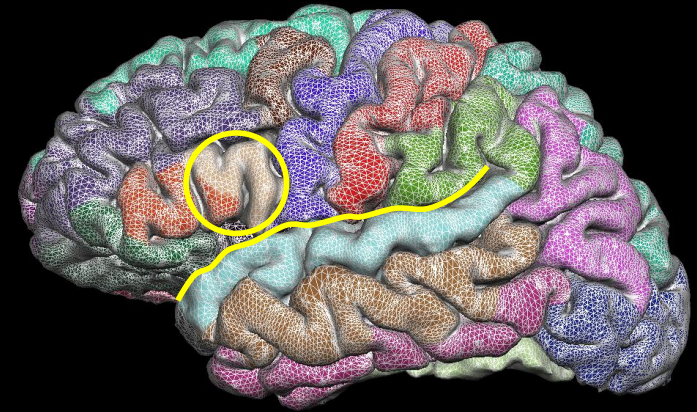
Discussion

- As predicted, the developmental trajectory of pars opercularis differed in PWS

- The developmental trajectory of Wernicke's area was comparable to controls

- Points to deficient neural resources for the development of speech sound representations in childhood

- Failure to complete synaptic pruning and resultant inefficient organization of speech sound maps in adulthood

- Cortical thickness is highly heritable in left perisylvian language regions (Thompson et al., 2001; Yoon et al., 2010)
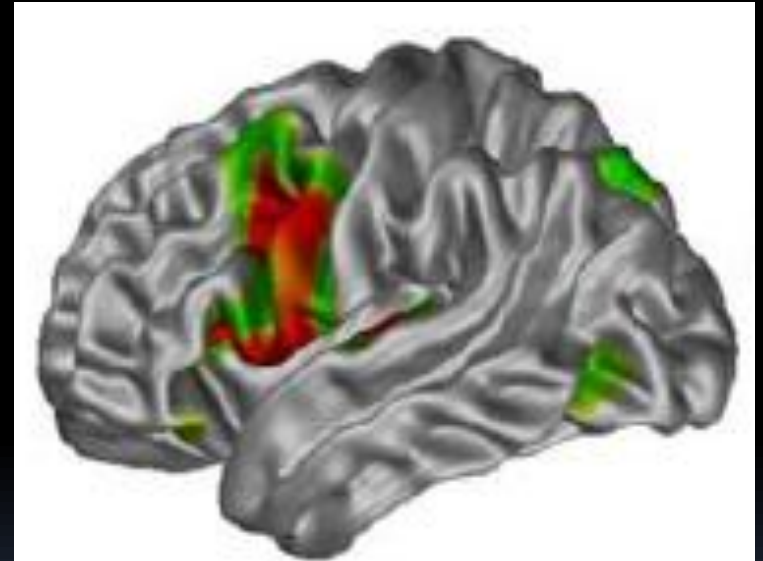
Pars opercularis: A key region of the aberrant neural mechanism for stuttering?

- Theory
  - PWS are unable to form and properly read out speech sound commands
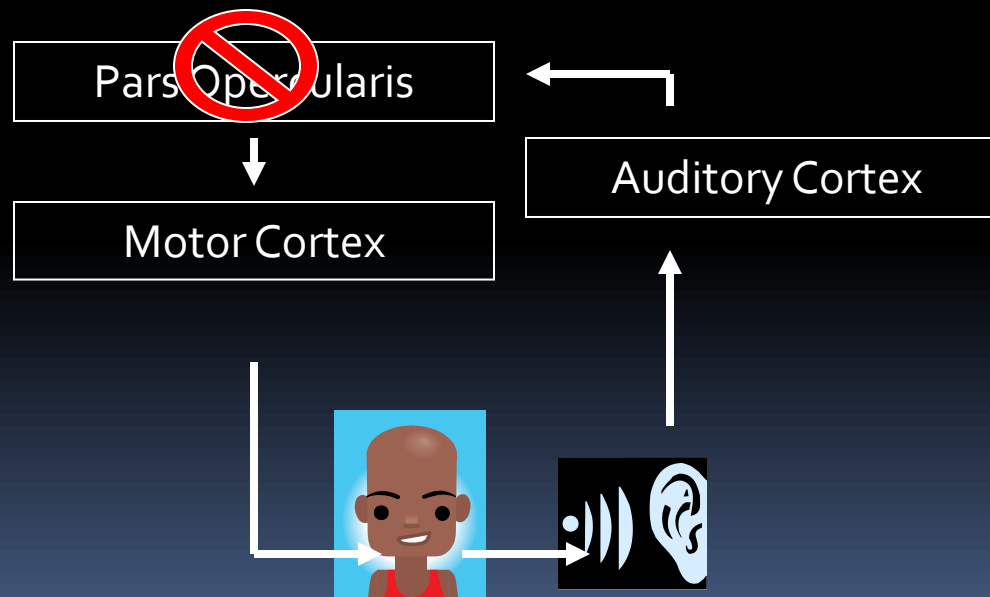
Outline

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    - Volume
    - Thickness
    - Connectivity
  - Function (Neurophysiology)
    - MEG
    - fMRI

Neurophysiological Differences

- Functional
  - a reduction in auditory cortex activation accompanied by the presence of increased activation in speech motor related cortex (Fox et al., 1996, 2000; Brown et al., 2005 ;De Nil et al., 2008)

- Interpretation
  - interaction between motor and auditory cortices may differ (Brown et al., 2005; Ludlow & Loucks, 2003; Max et al., 2004; Neilson & Neilson, 1987)

CON

AWS

a.

e.

Braun et al. 1997

Speech Induced Auditory Suppression
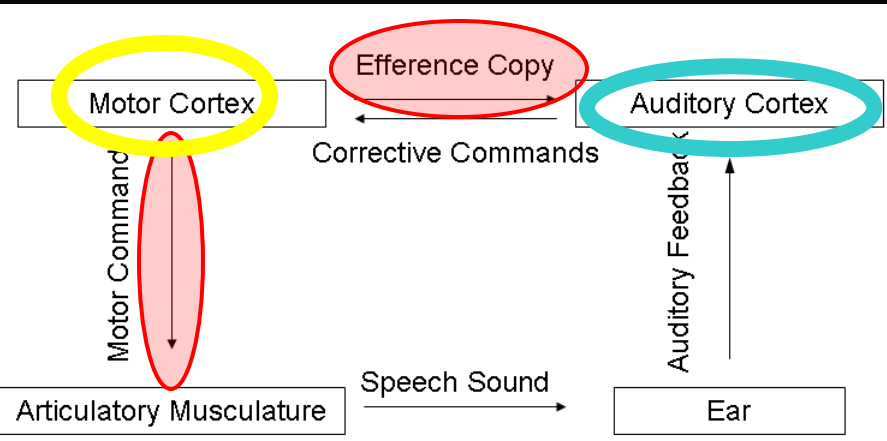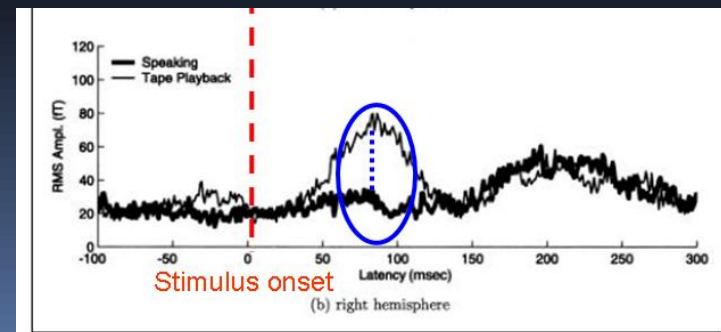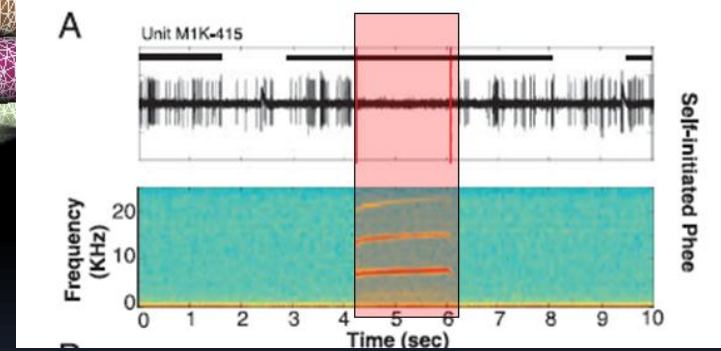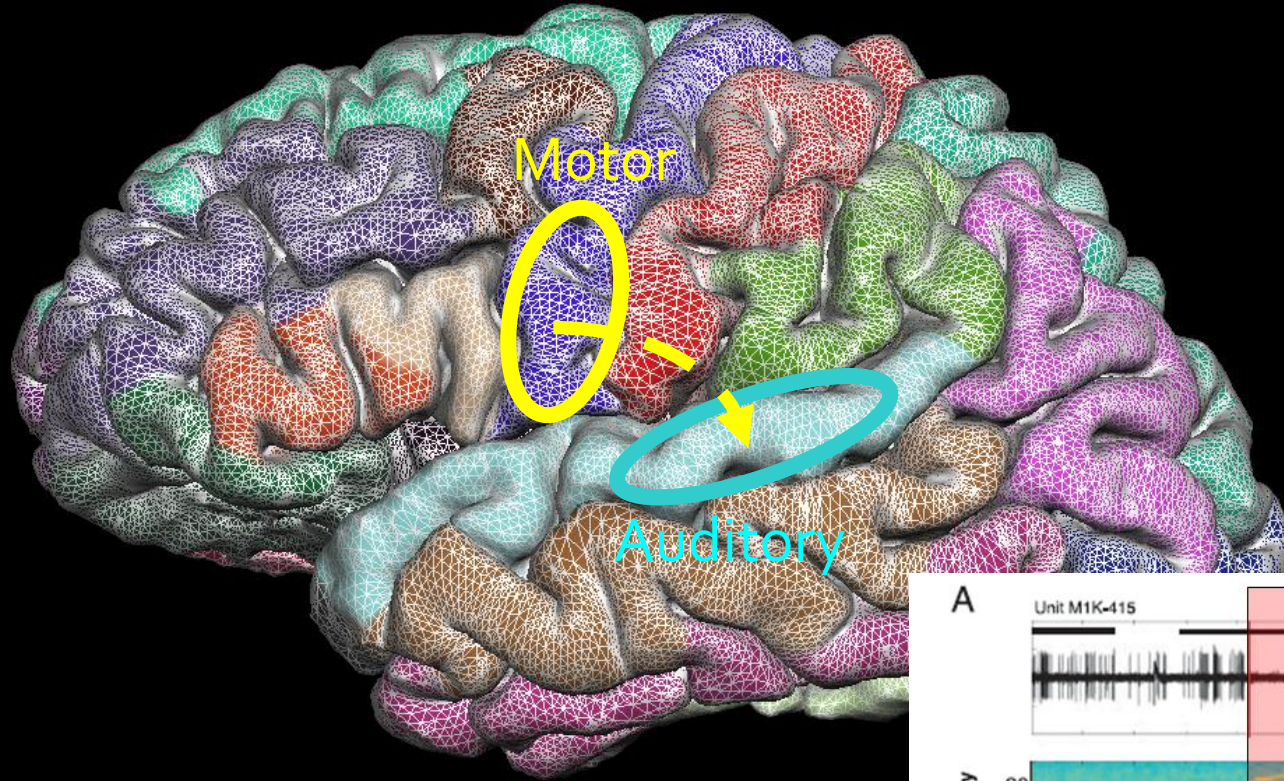
Speech Induced Auditory Suppression
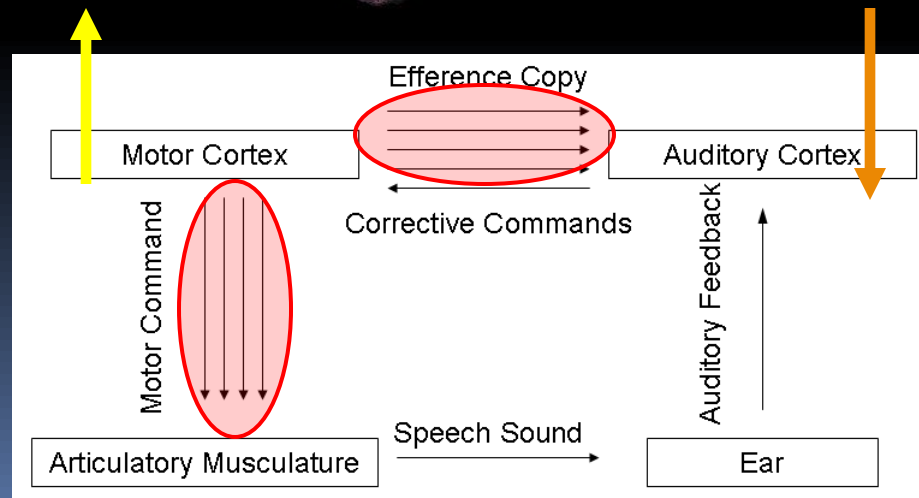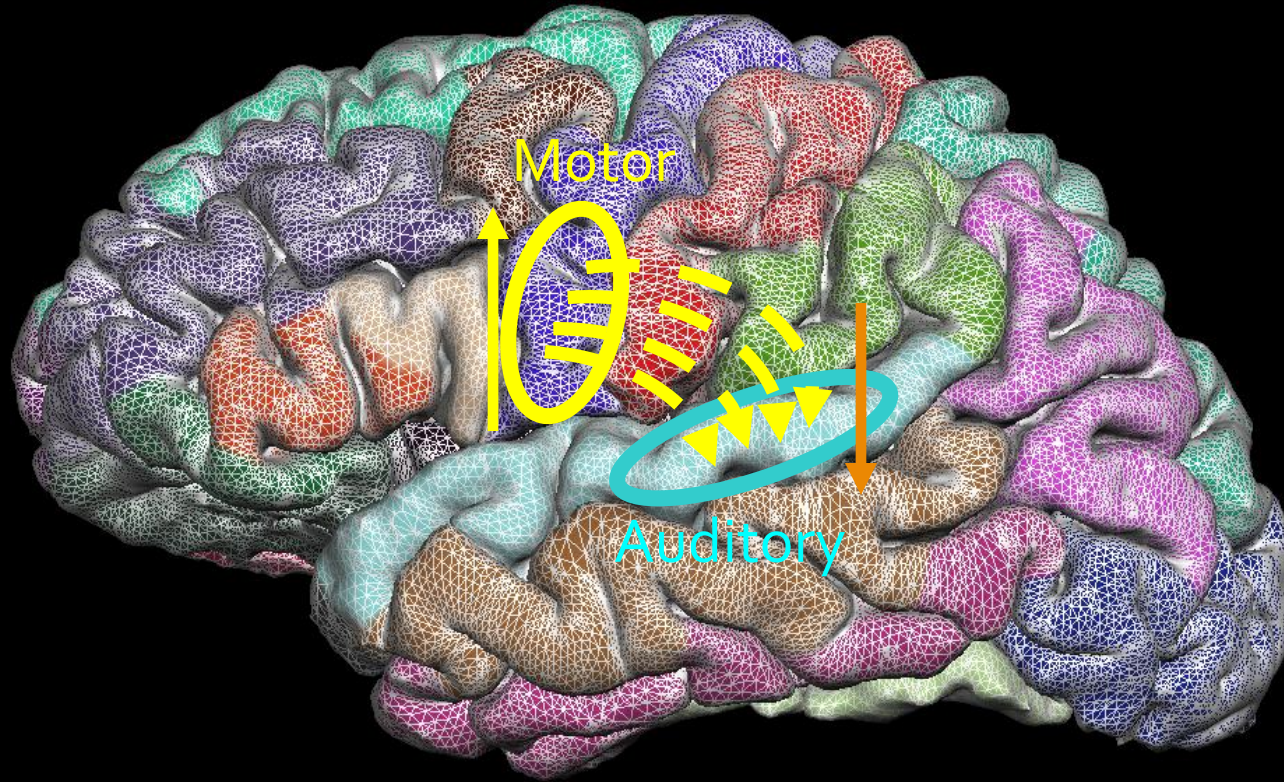
Research Questions

1. Do AWS have neurophysiological differences in auditory feedback processing during speech production compared to normal adults?

   a. Speech induced suppression will be increased in AWS relative to ANS.

   b. The peak latency of the auditory responses will differ in AWS.

2. Do CWS have neurophysiological differences in auditory feedback processing during speech production compared to normal children?

   a. Speech induced suppression will be increased in CWS relative to CNS.

   b. The peak latency of the auditory responses will differ in CWS.

Auditory evoked fields to vocalization during passive listening and active generation in adults who stutter

Deryk S. Beal [a,*], Douglas O. Cheyne [b,c,d], Vincent L. Gracco [e,f,g], Maher A. Quraan [b], Margot J. Taylor [b,c,d], Luc F. De Nil [a,b,h]

- **Participants**
  - 12 men who stutter (mean = 32.1 years; s.d. = 7.9)
    - Severity SSI-3 ranged from 8 - 44
  - 12 fluently speaking mean (mean = 32.9; s.d. = 7.4)
- **Data Acquisition**
  - Structural MR: T1 weighted
  - Functional MEG: Recorded continuously (2500Hz sample rate, DC-200 Hz bandpass, third-order spatial gradient noise cancellation)

Data Acquisition

<u>Anatomic Image Acquisition</u>

- 1.5-T Echospeed MRI system (GE Medical Systems, Milwaukee, WI), 8-channel head coil

- T1-weighted 3D inversion recovery-prepared FSPGR sequence; axial slices

<u>Functional Image Acquisition</u>

- Magnetic field responses were recorded continuously
  - (2500Hz sample rate, 0-200 Hz bandpass, third-order spatial gradient adapted noise cancellation)
  - CTF Omega 151 channel whole head MEG
- In-the-ear phones to listen to tones and vowels
- Microphone was placed directly in front of the participants

Task Summary

1. Listen tone

2. Listen to playback of vowel /i/

3. Speak vowel /i/

1.Listen tone

ISI 2500-3000ms

1 KHz   1 KHz   1 KHz   1 KHz   200 rep

50ms   50ms   50ms   50ms

+

2. Listen vowel /i/

ISI 2500-3000ms

/a/   /a/   /a/   /a/   200 rep

500ms   500ms   500ms   500ms
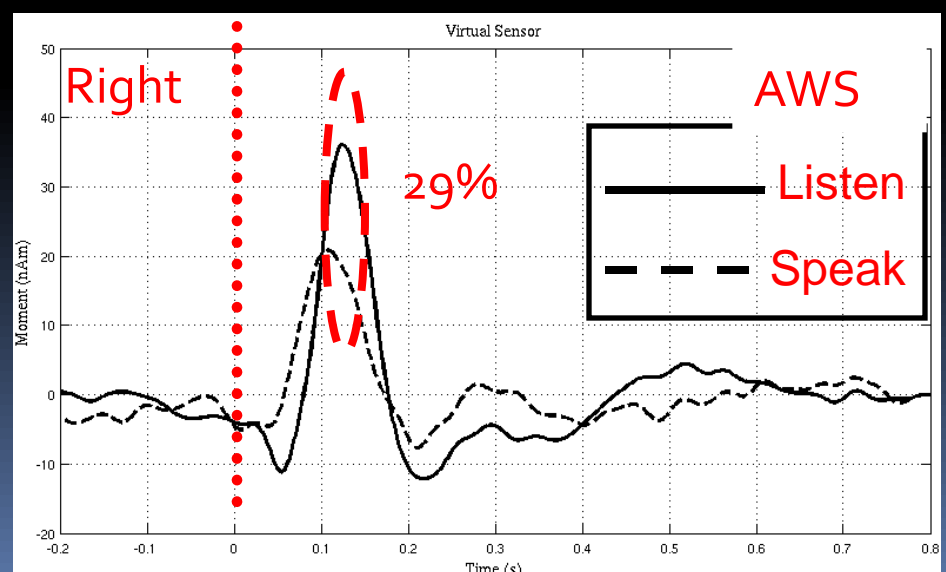
+

3. Speak vowel /i/

Visual

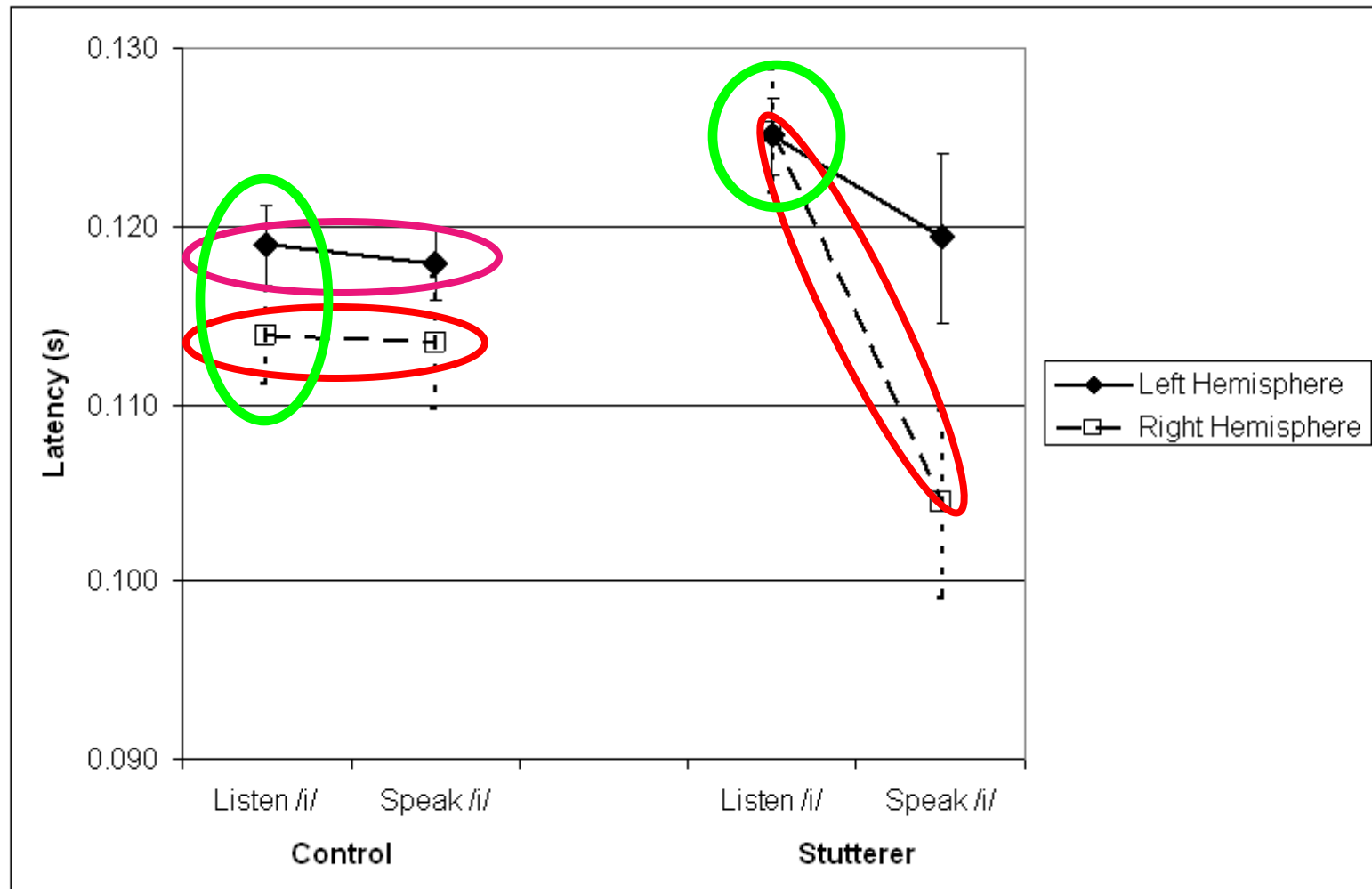* * * *   * * * *   200 rep

500 ms   500 ms
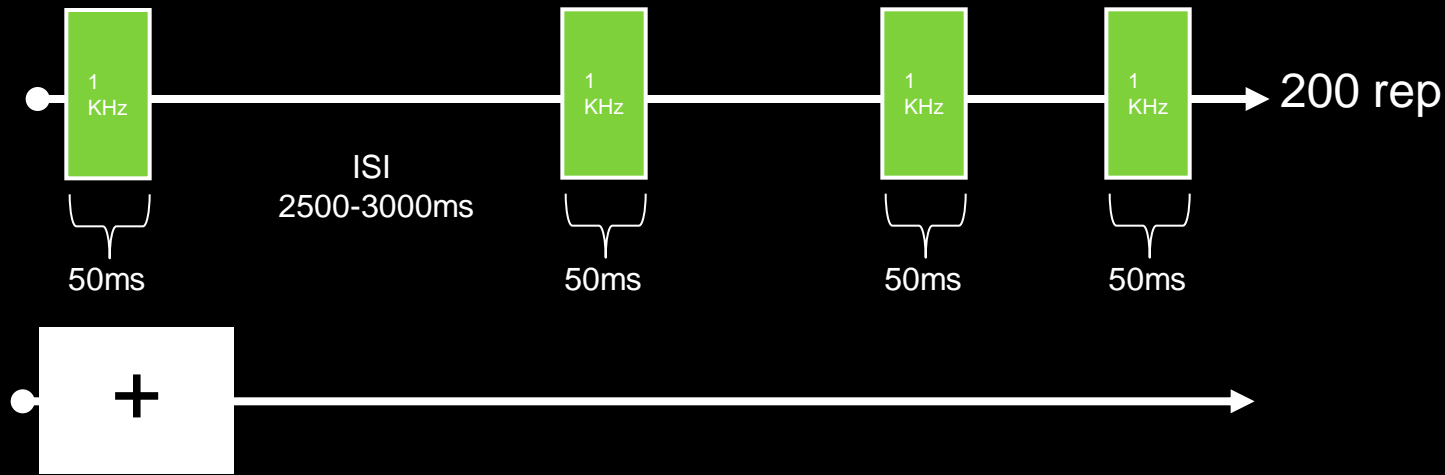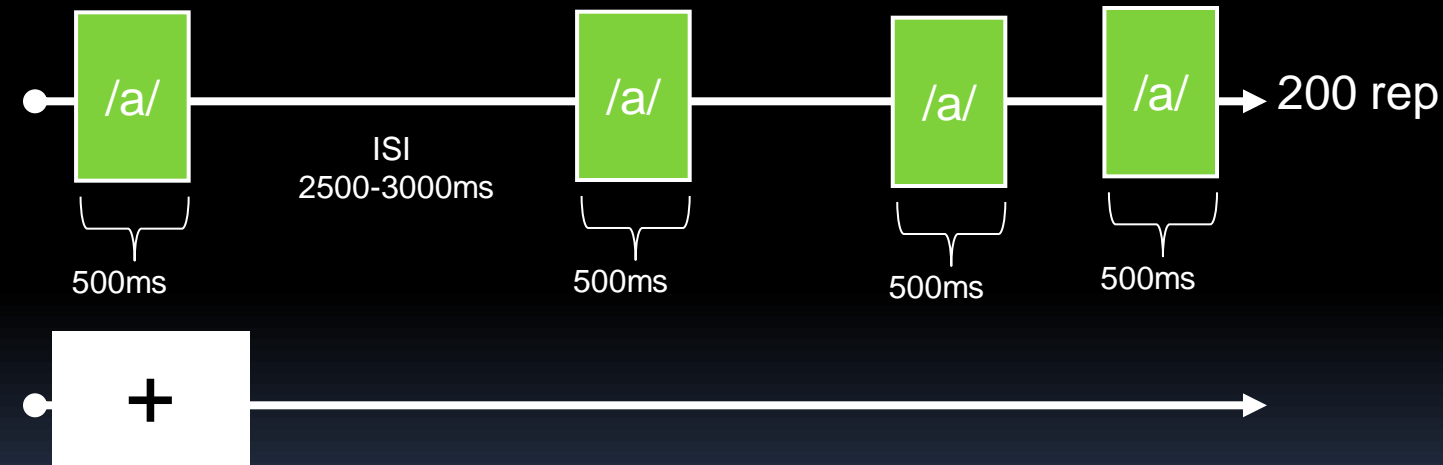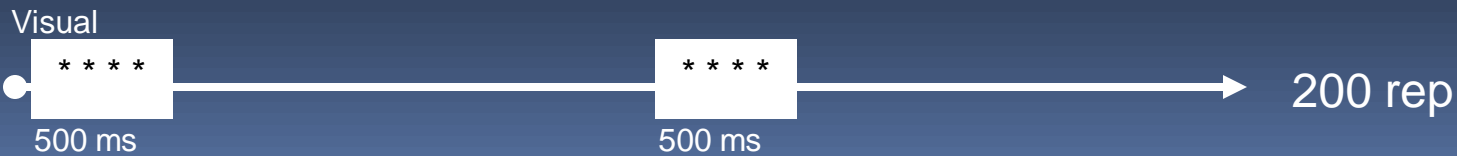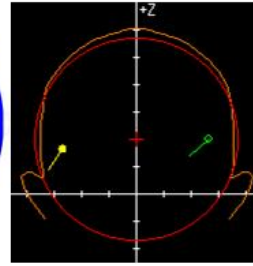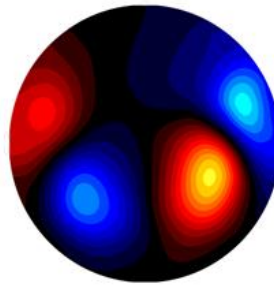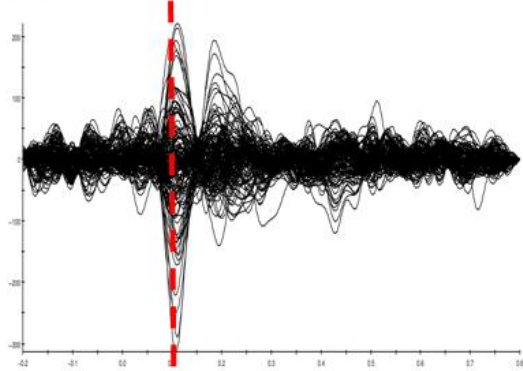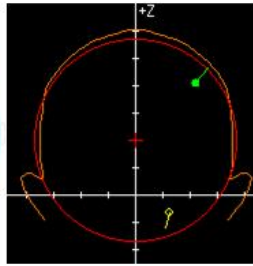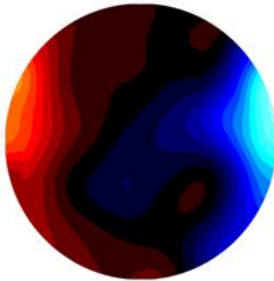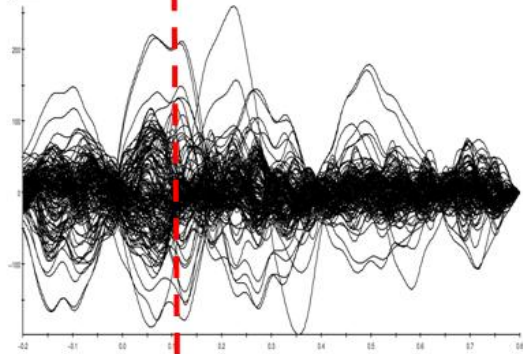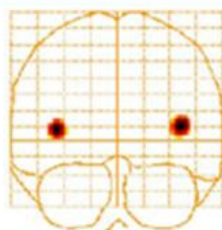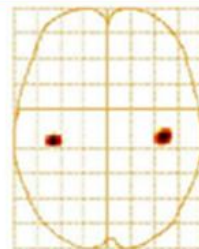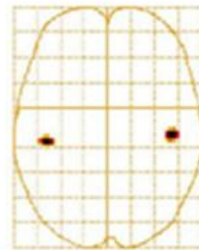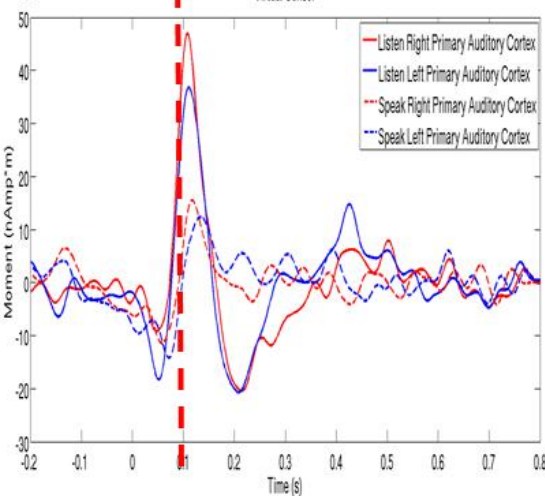
Beamformer Artifact Suppression

- Representative data from a single subject

- A. listen vowel DPF

- B. speak vowel DPF

- C. vowel BF & VS
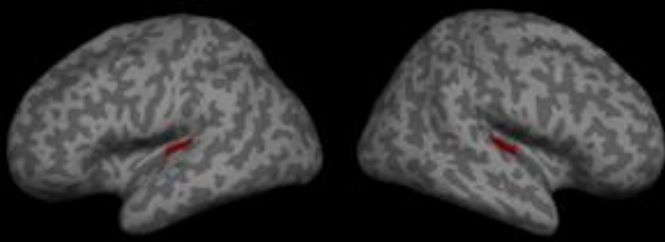
Hypothesis: Speech induced suppression will be increased in AWS relative to controls.
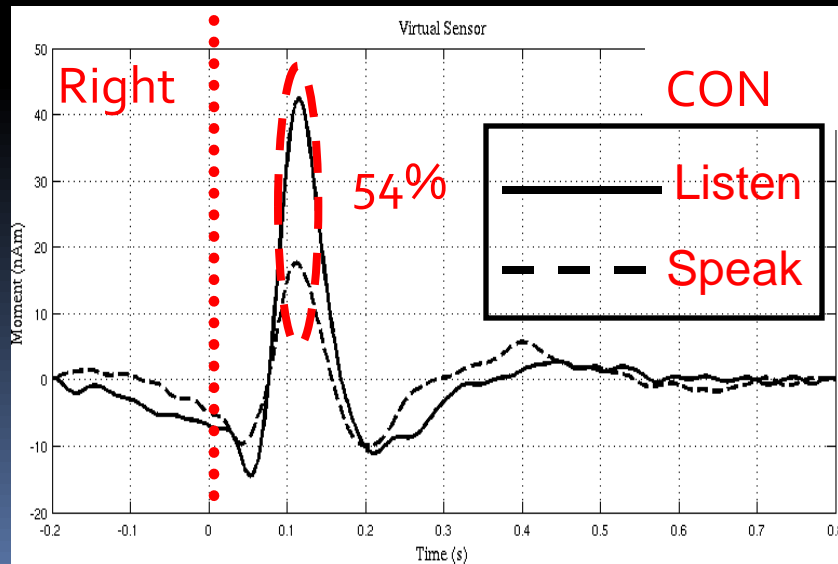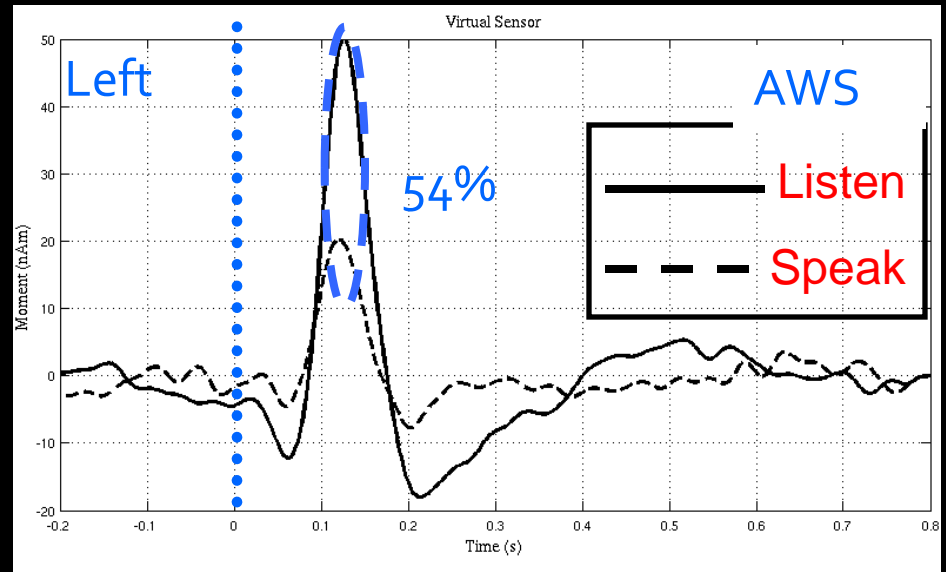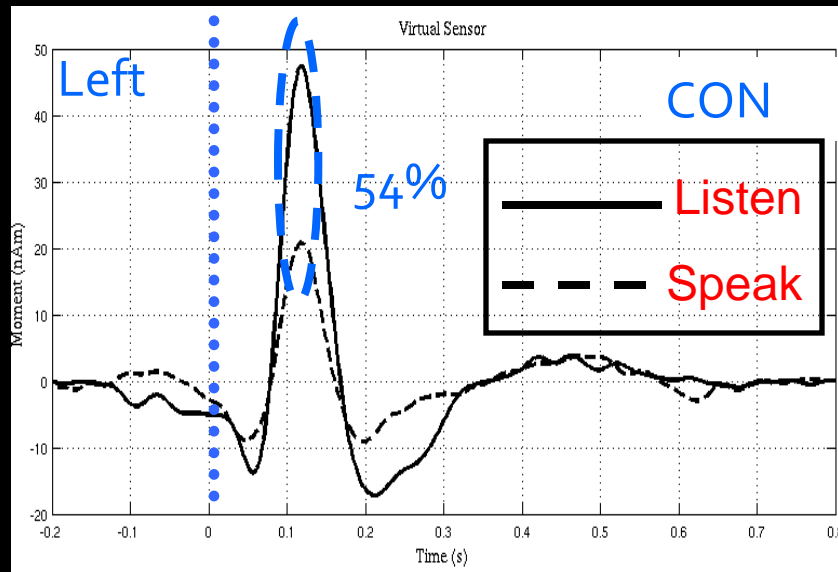
Hypothesis: The latencies of the evoked auditory responses will differ in AWS relative to ANS.
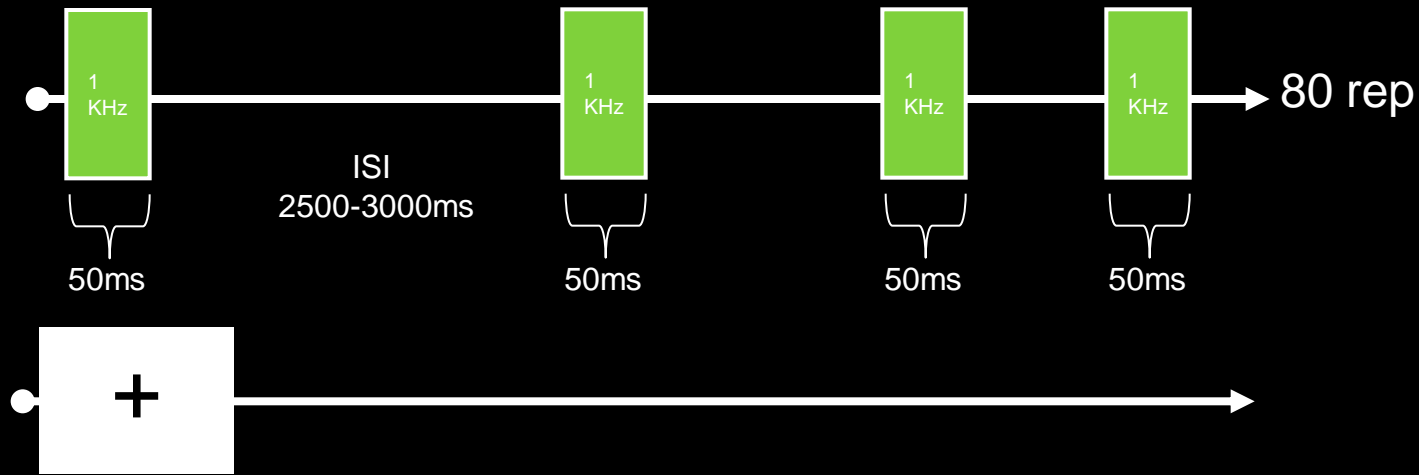
Speech-induced suppression of evoked auditory fields in children who stutter
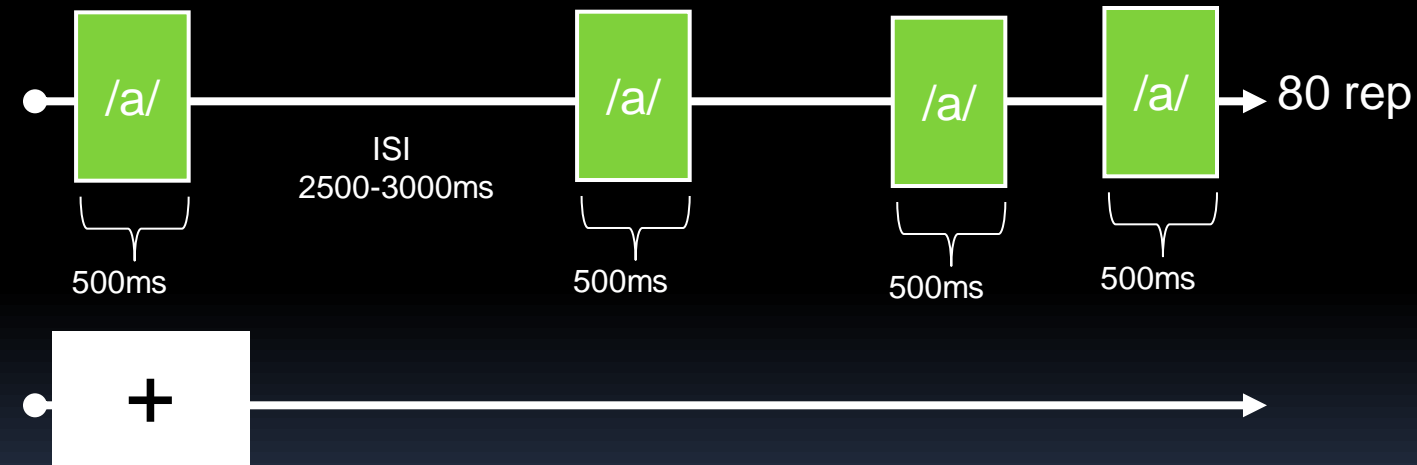
Deryk S. Beal [a,*], Maher A. Quraan [b], Douglas O. Cheyne [b,c,d], Margot J. Taylor [b,c,d], Vincent L. Gracco [e,f,g], Luc F. De Nil [a,b,h]

- **Common criteria:**
  - 11 Controls (*M* = 119 months; *s.d.* = 22 months) & 11 CWS (*M*= 114 months; *s.d*. = 18 months)
  - Right handed
  - English as primary language
  - Negative history of speech, language or hearing problems.
  - Speech, language and hearing screening by an s-lp

- **Specific criteria for CWS**
  - Onset of stuttering in childhood (pre-puberty).
  - A minimum of 3% within-word disfluencies in at least one of two speaking conditions (reading, conversation).
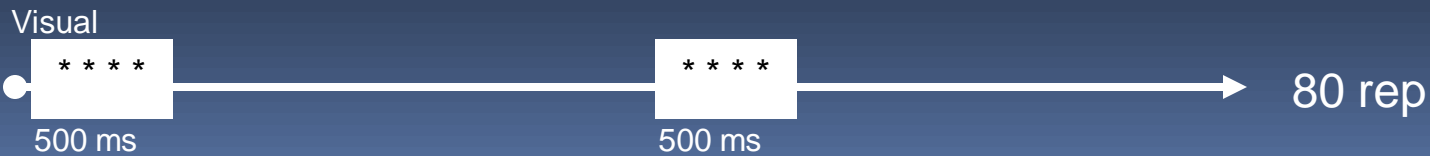 - Mild, moderate or severe on the Stuttering Severity Index (Riley, 1994).
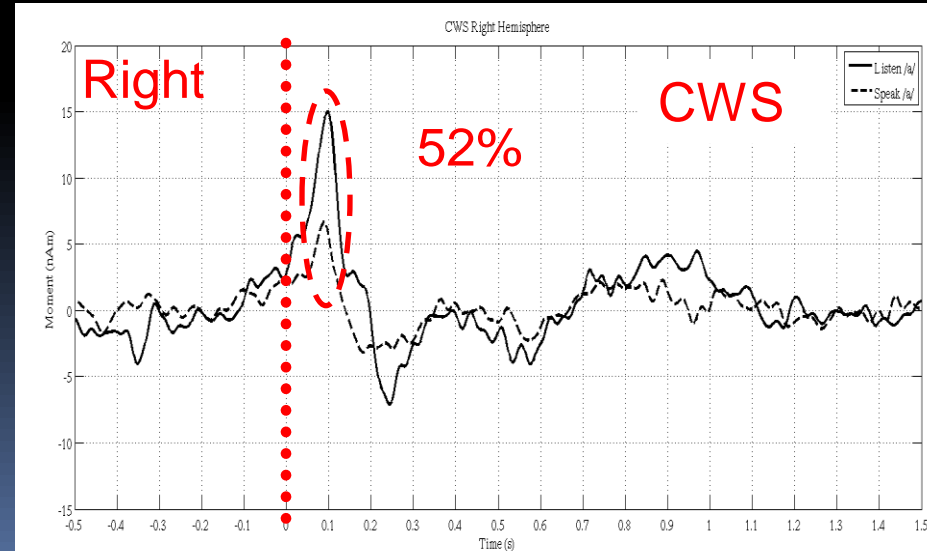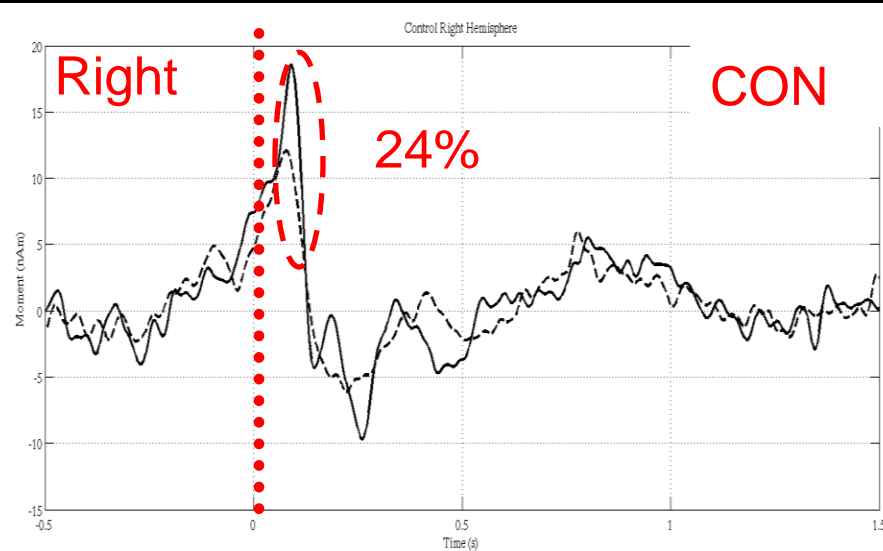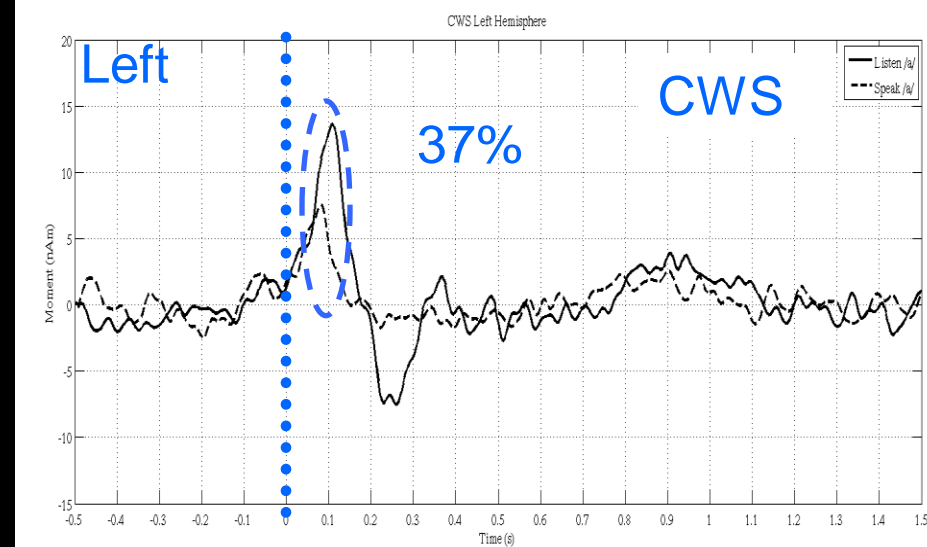
1. Listen tone

1 KHz | 1 KHz | 1 KHz | 1 KHz → 80 rep

ISI
2500-3000ms

50ms · 50ms · 50ms · 50ms

+

2. Listen vowel /a/

/a/ | /a/ | /a/ | /a/ → 80 rep

ISI
2500-3000ms

500ms · 500ms · 500ms · 500ms

+

3. Speak vowel /a/

Visual

* * * *   * * * *   → 80 rep

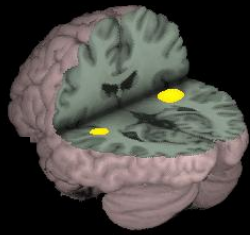500 ms   500 ms
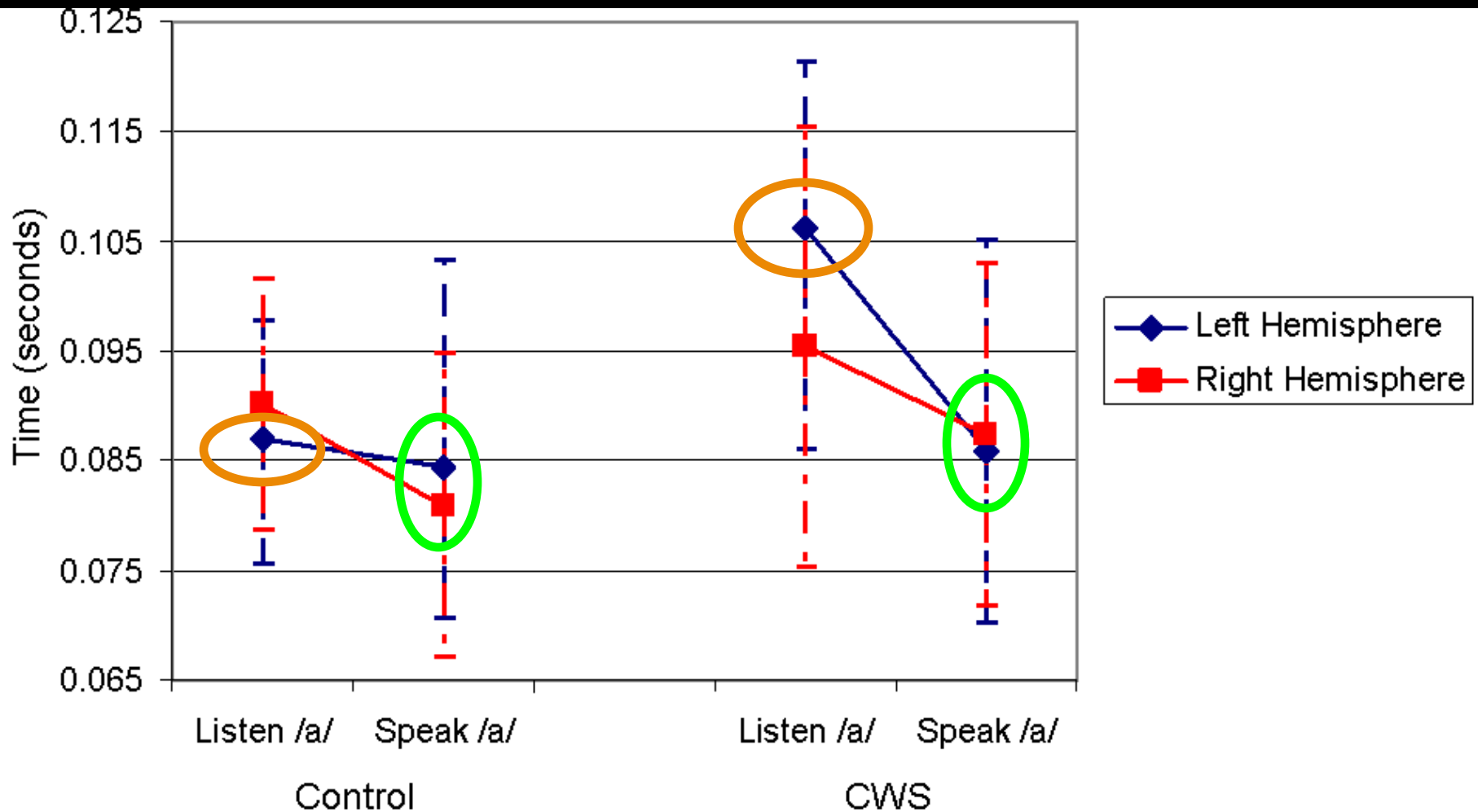
Speech induced suppression will be increased in CWS relative to controls.
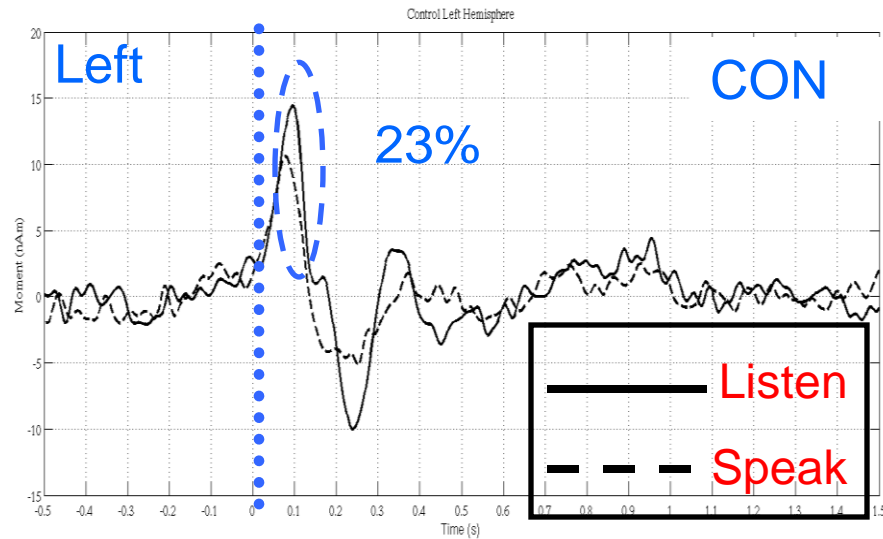
Hypothesis: The latencies of the evoked auditory responses will differ in CWS relative to CNS.
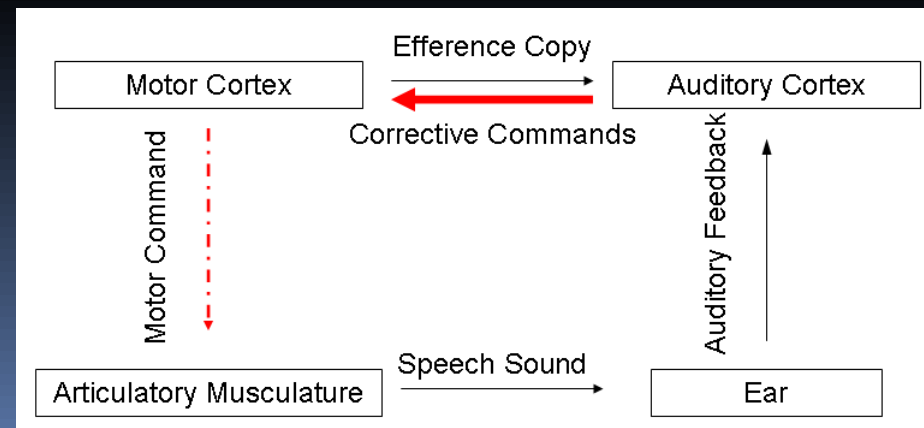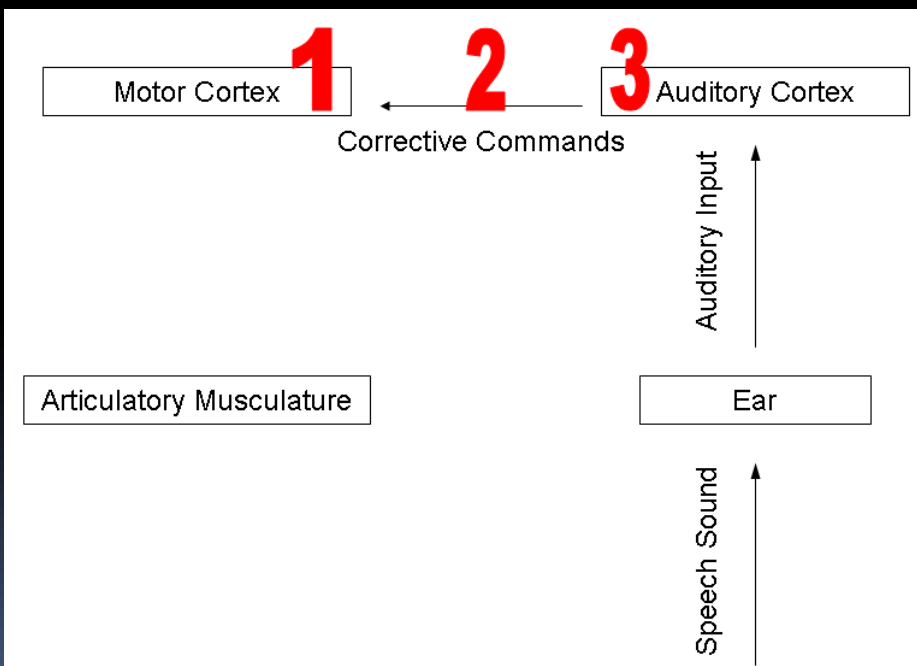
Implications

- **Adults and children who stutter did not demonstrate increased speech induced auditory suppression**

  - **It is unlikely that the pattern of increased motor activity and reduced auditory activity observed in PET & fMRI studies of adults who stutter is due to increased efference copy transmission**
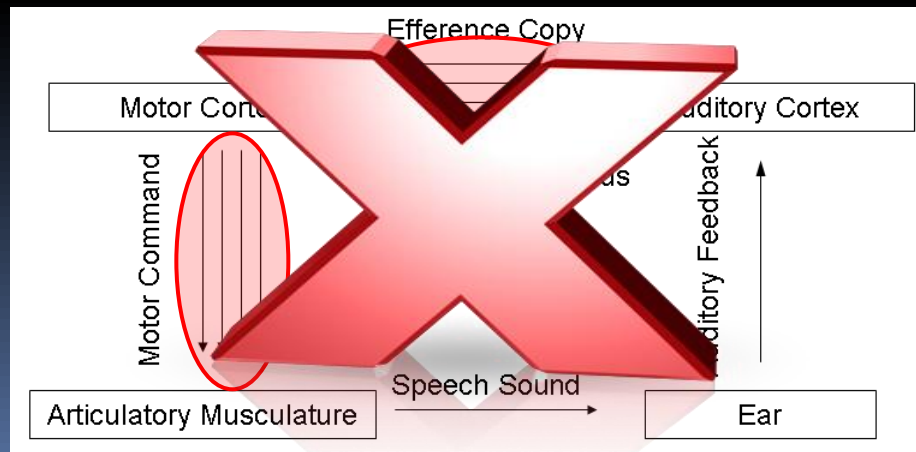
Conclusions

- **Rather, the importance of neural timing differences in auditory cortex for speech sound processing was revealed**
  - Adults and children who stutter had delayed auditory responses for passively listening to speech stimuli
  - Adults who stutter had shorter right hemisphere auditory responses for speaking

- **Taken together with grey matter abnormalities in speech cortex, the auditory processing delays support the ideas that:**
  - Children who stutter have difficulty establishing the neural representations of speech sounds needed for fluent speech
  - Adults who stutter have difficulty maintaining/updating the neural representations of speech sounds and adjust auditory feedback processing of speech to accommodate

Results of kinematic variability, auditory perturbation and sequence learning studies

- Slides removed as data are in process of publication. Please email dsbeal@bu.edu for more information.

Summary

- People who stutter have been found to have an abnormal trajectory of grey matter development in the left pars opercularis (Beal et al., 2007; submitted)
- People who stutter have been found to have reduced white matter connectivity in pathways underlying the left pars opercularis (Cai, Beal et al., in preparation; Chang et al., 2008, Watkins et al., 2008)
- Direct and indirect evidence that abnormal structure is related to reduced stability of neuro-motor programs (Beal et al., 2010, 2011; Cai, Beal et al., in preparation).
- This deficit likely does not exist in isolation but may be the result of an abnormal motor learning system (Beal et al., in progress)

Conclusions

- Emerging field of developmental cognitive neuroscience
  - Advantages:
    - It is now possible & acceptable to study children using neuroimaging tools and paradigms
    - A literature exists to support a large, longitudinal study with the goal of understanding brain development in children who stutter
- Understanding neuro-motor control and learning is important for improving treatment

University of Toronto

Luc De Nil
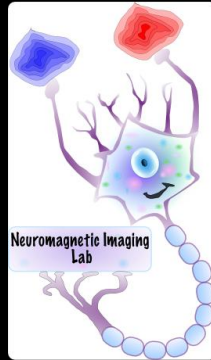
Doug Cheyne

Margot Taylor

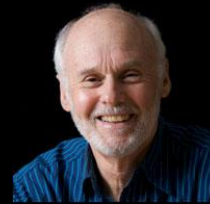Vince Gracco

Bob Harrison

Maher Quraan
Marc Lalancette
Travis Mills
Paul Ferrari
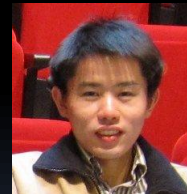Sonya Bells
Sophie Lafaille

Boston University / MIT / MGH

Frank Guenther

Joe Perkell

Jason Tourville

Shanqing Cai

Satra Ghosh