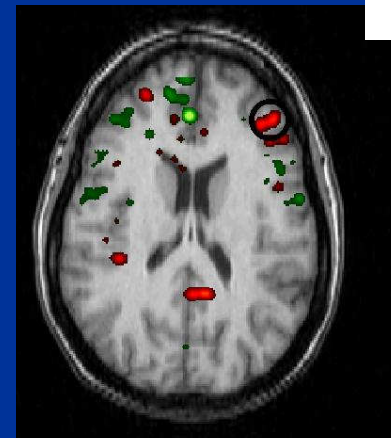
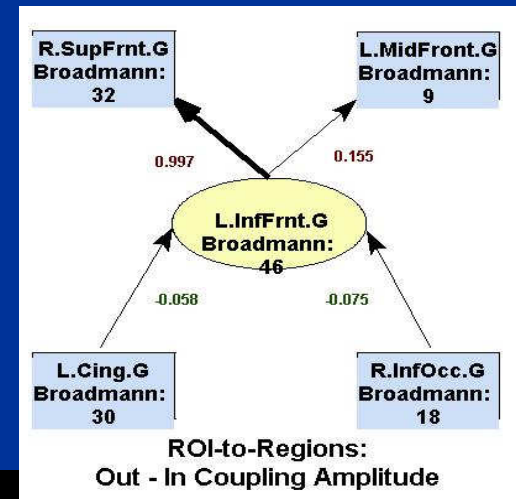
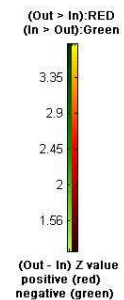


Choral Speech Effects on Stuttering

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Disclosures

No Disclosures

But some Biases

- ISACM Board Member
- ACMEGS Board Member

Understanding How Patients who Stutter Processes Language

Normal speakers
From
Cognition / Receptive
Wernicke's AREA

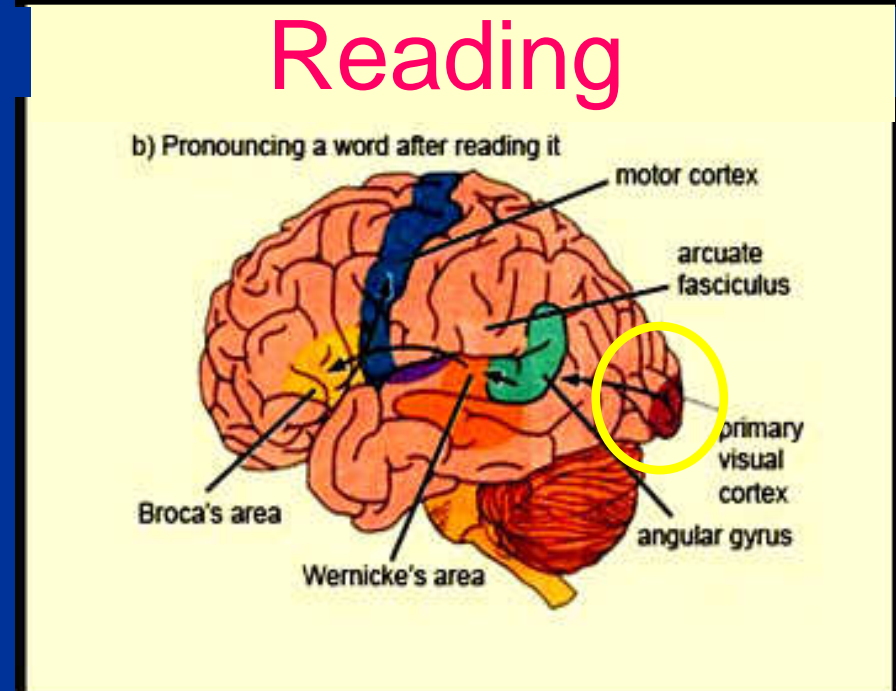
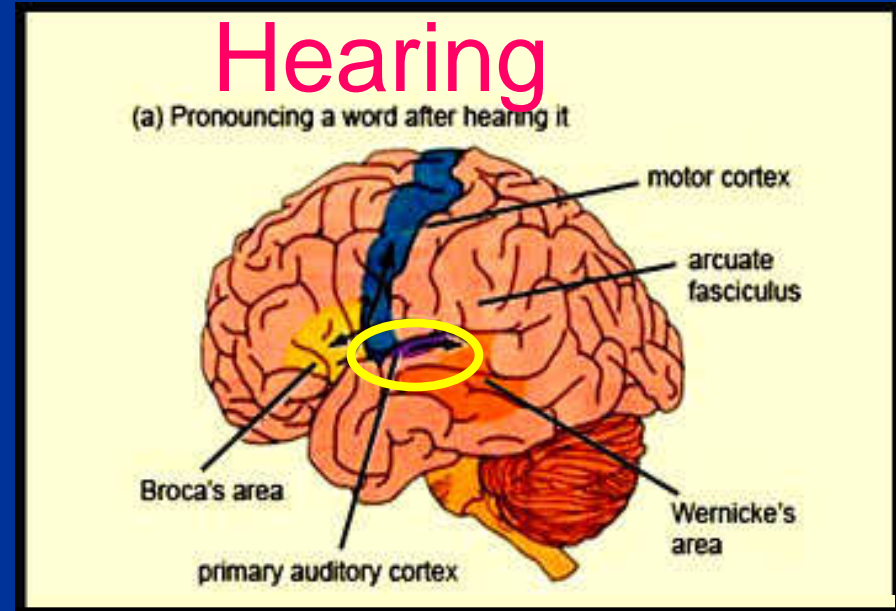
superior temporal gyrus (BA 22)

angular gyrus (BA 39)

supramarginal gyrus (BA 40)

To
Production / Expressive
Broca's AREA

pars opercularis and pars triangularis
of the inferior frontal gyrus (BA 44 and 45)



Stuttering

- Is a debilitating communication disorder
- This disorder disrupts the forward flow of speech
- According to The Stuttering Foundation, 68 million people worldwide stutter – that's roughly 1 percent of the world's population (7billion)
- Four times more boys than girls are affected by this disorder (Yairi 1996).
- There are lots of Success stories.
 - Marilyn Monroe, Winston Churchill
 - King George VI of England whose stuttering woes were depicted in the award winning movie "The King's Speech" (Howell 2011).

Language organization in Patients who Stutter (PWS)

- Identify the neural processes underlying stuttering
- A “dynamic interplay among complex cortical and subcortical systems”, involving areas of planning, production and monitoring (Ludlow 2000; Ingham 2001; 2004)
- Although there is agreement that there are likely many neural subsystems that comprise the disorder of stuttering, there has not been agreement about what subsystems are involved and how they are connected (Braun 1997; Salmelin 2000; Ingham 2001; Brown 2005).

Functional MRI and PET studies

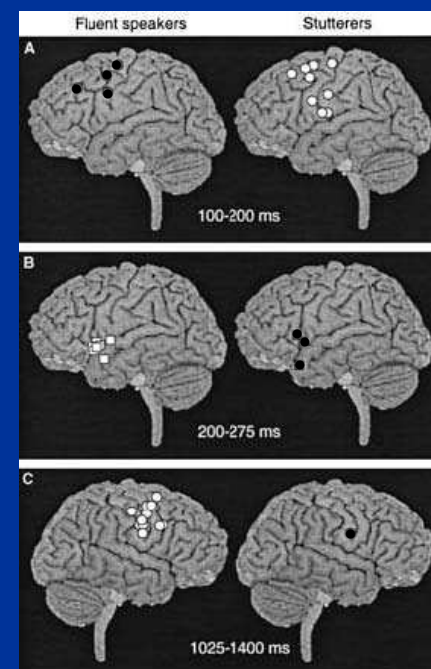
- A meta-analysis of speech production during single-word reading studies (PET and fMRI) on controls and PWS (Brown 2005) identified activation in
 - inferior frontal gyrus (IFG)
 - superior temporal gyrus (STG)
 - motor cortex --- OVER activated in PWS
 - premotor cortex --- OVER activated in PWS
 - supplementary motor area --- OVER activated in PWS
 - Rolandic operculum
 - lateral cerebellum
 - auditory cortex
- These neuroimaging techniques offer a comprehensive view of brain activity and helped to point out different areas of cortical activation between Controls and PWS
- Though fMRI provides higher temporal resolution than PET, it still does not provide the temporal resolution that is necessary for connected speech to be closely examined.
- Temporal resolution should be in the millisecond range so identification of the direction of information flow can be detected.

EEG Studies

- Event-related brain potentials (ERPs) revealed that language processing is subtly altered in PWS, even in the absence of overt speech production requirements (Weber-Fox, 2001; Cuadrado & Weber-Fox, 2003; Weber-Fox et al., 2004). These studies utilized visual language stimuli and revealed that, despite possessing language abilities that are within normal limits, some neural processes peaking after 250 ms are atypical in PWS.
- Early latency cortical potentials (N100, N180, P200), thought to be more closely related to sensory, perceptual processes (Mangun & Hillyard, 1991), did not distinguish PWS and normal fluency readers (Cuadrado & Weber-Fox, 2003; Weber-Fox, 2001; Weber-Fox et al., 2004).
- In contrast, endogenous, longer latency ERPs elicited in PWS were characterized by reduced amplitudes on EEG.
- Both the N400 elicited by semantic anomalies and the late positivity (P600) elicited by verb-agreement violations were smaller in amplitude for PWS compared to normal fluency readers. Thus, processes associated with integration of word meaning (indexed by the N400, e.g., Kutas & Hillyard, 1980) and syntactic re-analysis (indexed by the P600, e.g., Friederici, Hahne, & Mecklinger, 1996; Hagoort, Brown, & Grotthusen, 1993; Neville, Nicol, Barss, Forster, & Garrett, 1991; Osterhout & Holcomb, 1992; Osterhout & Mobley, 1995) point to processing differences in PWS for both semantic and syntactic constraints, despite solid language skills indexed by standardized measures.

Past MEG Studies

- Salmelin and colleagues performed the first MEG study on PWS (Salmelin 1998). They found differences in cortical organization of the auditory response between AWS and fluent speakers.
- This same group performed a second MEG study to detect speech production during reading aloud (Salmelin 2000).
- Within the first 400 ms after seeing the word, processing in fluent speakers advanced from the left inferior frontal cortex (articulatory programming) to the left lateral central sulcus and dorsal premotor cortex (motor preparation).
- This sequence was reversed in the PWS, who showed an early left motor cortex activation followed by a delayed left inferior frontal signal.
- The **right frontal cortex** of stutterers was highly active during speech production but did not generate synchronous time-locked responses.
- These findings may reflect imprecise functional connectivity within the right frontal cortex and incomplete segregation between the adjacent hand and mouth motor representations in stutterers during speech production.

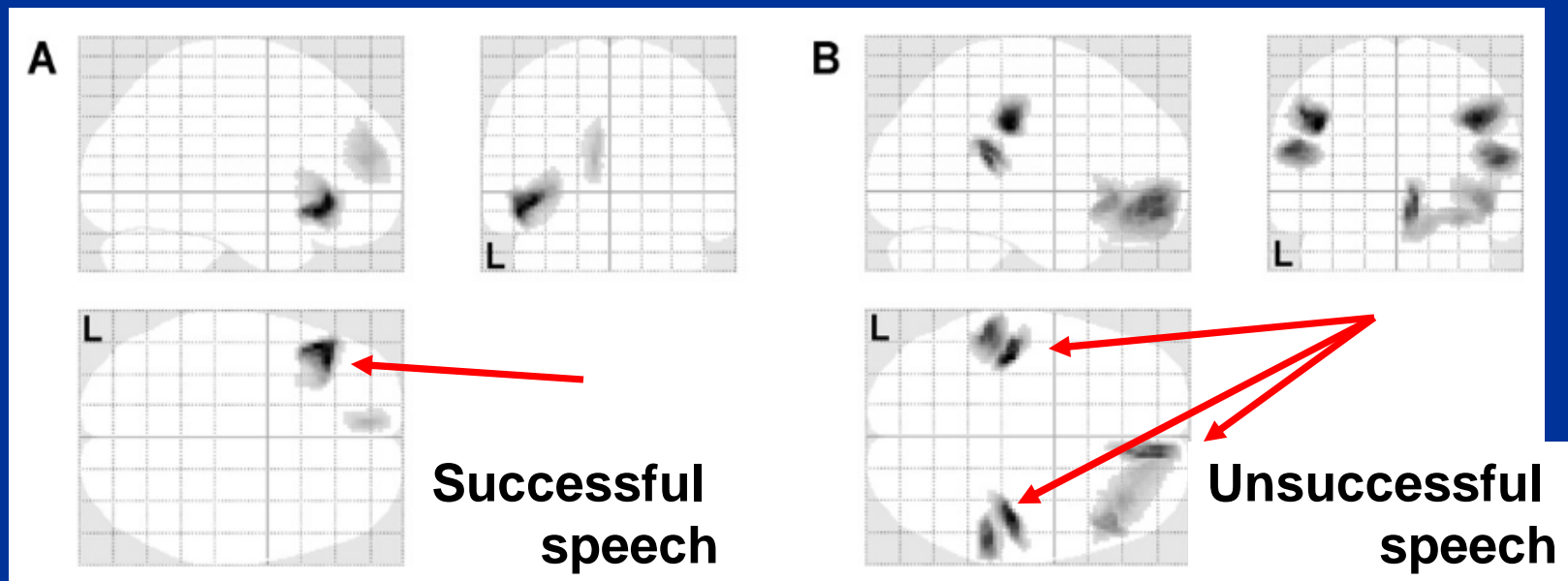


MEG studies continued

- The third MEG study found a lack of focused anticipation of verbal information during visually presented single words in PWS (Walla 2004). These results may be related to impaired focused attention or anticipation.
- A fourth MEG study of auditory speech perception indicated language processing differs in PWS. Biermann-Rubin and colleagues (2005), detected alternate language processing pathways during speech perception prior to overt repetition of a spoken word and sentence, and a sentence transformation task. **PWS had greater activation of left inferior frontal areas, thought to be important for speech preparation, during the temporal window of 95–145 ms post-word and sentence onsets.** In addition, between 315–1000 ms post-stimulus, activations of the right rolandic areas, thought to be involved in sensorimotor processing, were larger for single-word compared to sentence tasks for the fluent readers, but the opposite pattern was seen for the PWS. Their results suggest that activation in the **left inferior frontal and right rolandic areas in PWS differs** from that in controls during speech perception.
- The fifth MEG study (Kikuchi 2011) found auditory sensory gating (P50m suppression) was impaired in the left hemisphere during basic auditory input processing could result in abnormal speech processing. They hypothesize that the functional and structural reorganization of the right auditory cortex maybe a compensatory mechanism for impaired left auditory cortex function in AWS.
- The 6th MEG study found speech induced suppression of auditory evoked fields in children who stutter (CWS) (Beal 2011). CWS had a delayed auditory M50 peak latency to vowel sounds compared to children who do not stutter indicating a possible deficiency in their ability to efficiently integrate auditory speech information.

Most recent MEG case study

- A unique case study by Sowman and colleges in Australia allowed the comparison of brain activations leading up to a block with those leading up to successful production.
- Preceding a block there is significantly less activation of the left orbitofrontal and inferiorfrontal cortices.
- Furthermore, there is significant extra activation in the right orbitofrontal and inferiorfrontal cortices, and the sensorimotor and auditory areas bilaterally.



HFH MEG study

- We used MEG to explore the neural connections in people who stutter (PWS) compared to fluent speaking control subjects.
- Two areas of significance between PWS and controls:
 - Activation patterns in the brain during speech tasks
 - With and without the speech easy treatment device
 - Functional brain network activity during resting state, measured by Coherence

Methods

- Subjects
 - 10 adults who stutter (AWS)
 - 7 control subjects matched for age and gender
- Data Collection
 - Verb generation task
 - Oral reading of single words
 - Rest state data was collected for 10 minutes while subjects were quietly lying on their backs, with eyes open

Activation tasks to measure:

Receptive to Expressive
Cognition to Production

SPOON

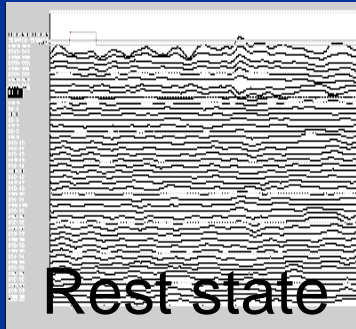
-Visual Verb Generation

?

-Visual word reading

Steps from MEG data to MEG Images

Data acquisition and preprocessing



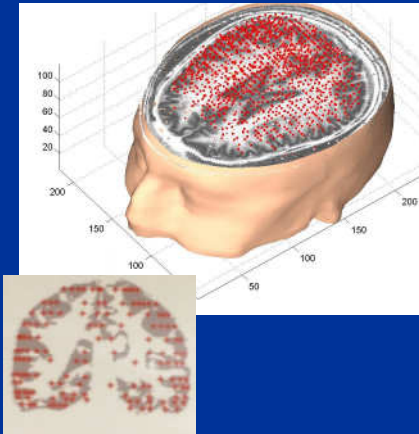
148 Magnetometer channels
Filter 3-50Hz



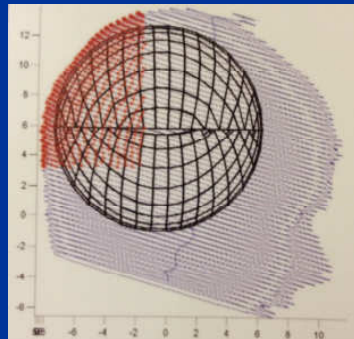
Coregistration of MEG with MRI



Cortical Model Constraining solution



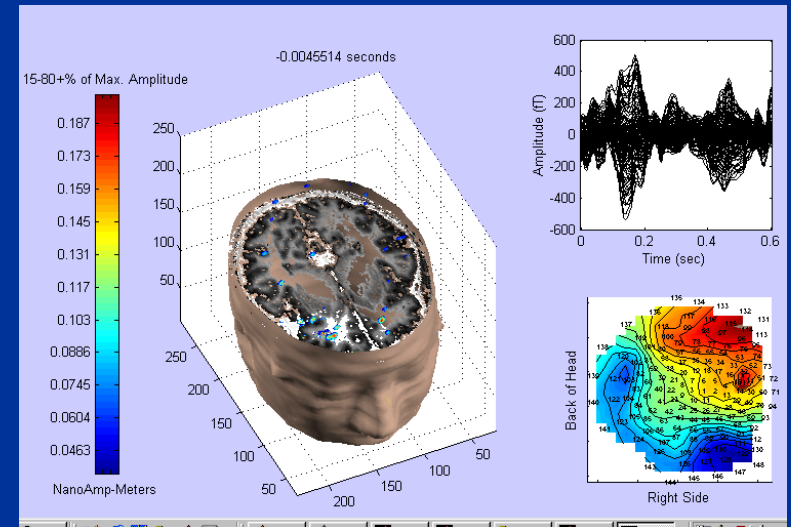
Forward Model Initial estimate



- Created from Volumetric MRI
- ~4000 cortical locations
- each with an x y z component
- Distribution matches cortical gray

A spherical model of the head exactly matched to local skull curvature for 6 different regions of the brain

Current Distribution Technique - MR-FOCUSS (Multi-Resolution FOCal Underdetermined System Solution)



MR-FOCUSS utilizes a recursively adapted sparse wavelet statistical operator that allows spatial resolution to be chosen appropriately for focal or extended sources. Control of focal imaging properties is achieved by specifying P in an l_p norm distribution template used to construct the wavelets. In addition, incorporation of a multi-resolution wavelet operator desensitizes the mathematical algorithm to noise, (regularization). An initial estimate of cortical activity is recursively enhanced to obtain the final imaging results.

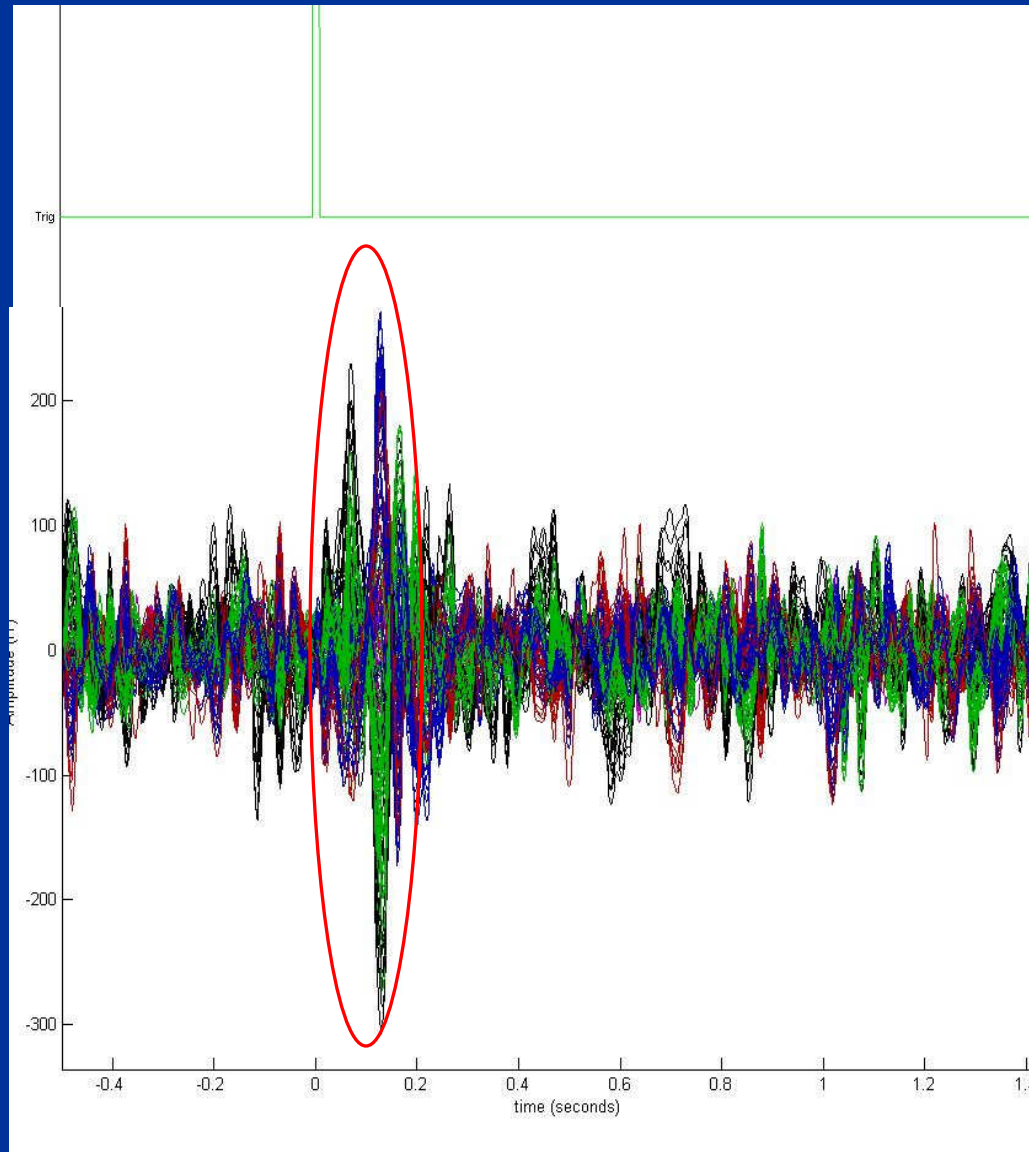
Initial Inspection of Early latency

- Initial peaks (<200 ms) basic Visual processing
- Early evoked fields were similar across all subjects.
- Visual Cortex activation latency comparisons had p-values greater than 0.05 (indicating that the comparisons were not statistically significant. This suggests the stuttering disorder does not lie in the ability to visualize words.

Reading Aloud - PWS

Trigger

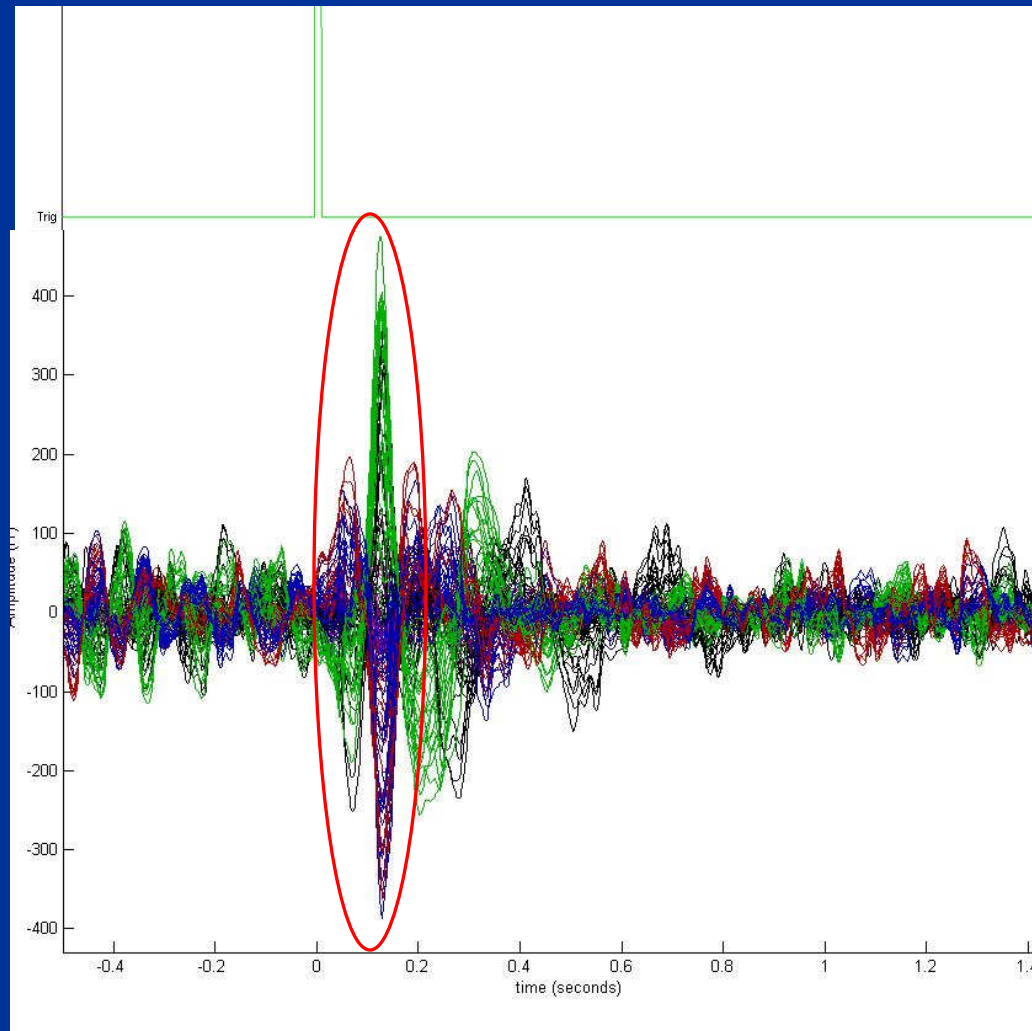
148
MEG



Reading Aloud - Fluent

Trigger

148
MEG



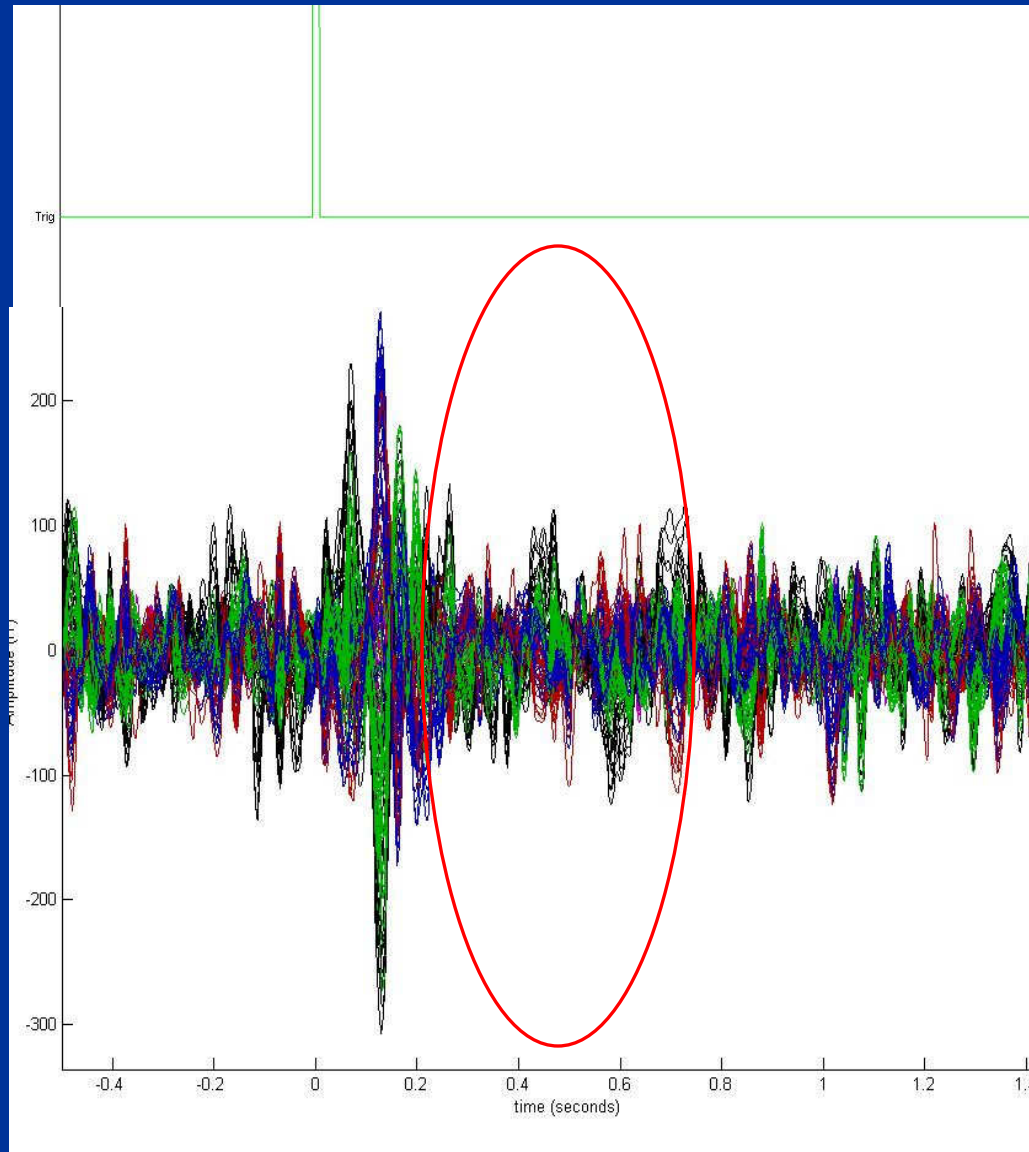
Initial Inspection of Long latency

- Long latency responses (> 200 ms after stimuli onset) evoked by language stimulation. In fluent speakers several peaks between 200-500 ms are seen but may extend to 750 ms or beyond
- Peaks were not as clear or symmetrical as the early latencies, since the Long latencies contains activity arising from multiple language areas
- The signals reflect varying contributions from multiple language areas including:
 - Wernicke's language area (superior temporal gyrus Brodmann's area (BA 22), the angular gyrus (BA 39), the supramarginal gyrus (BA 40)
 - Broca's language area (pars opercularis and pars triangularis of the inferior frontal gyrus (BA 44 and 45).
- Wernicke's Area activation latency comparisons had p-values greater than 0.05 (indicating that the comparisons were not statistically significant. This suggests the stuttering disorder does not lie in the ability to process/comprehend words.

Reading Aloud - AWS

Trigger

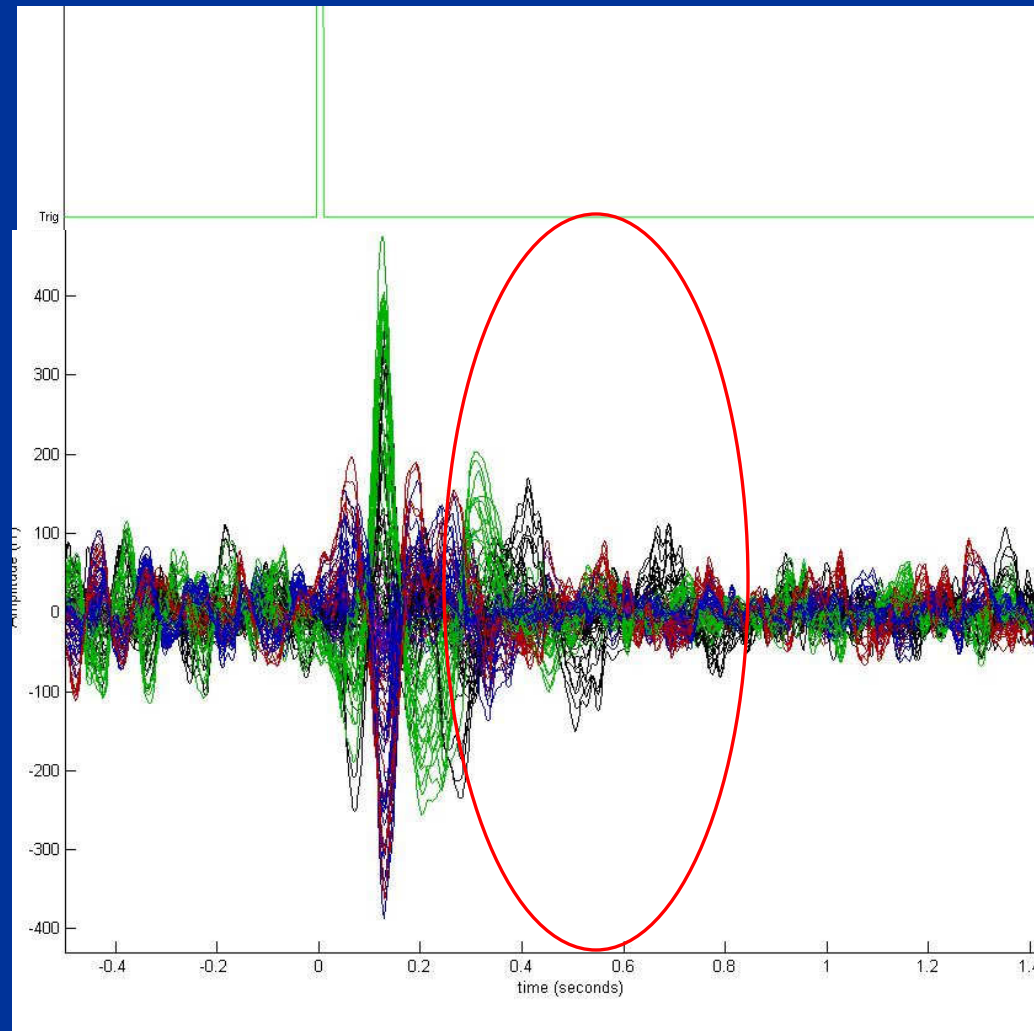
148
MEG



Reading Aloud - Fluent

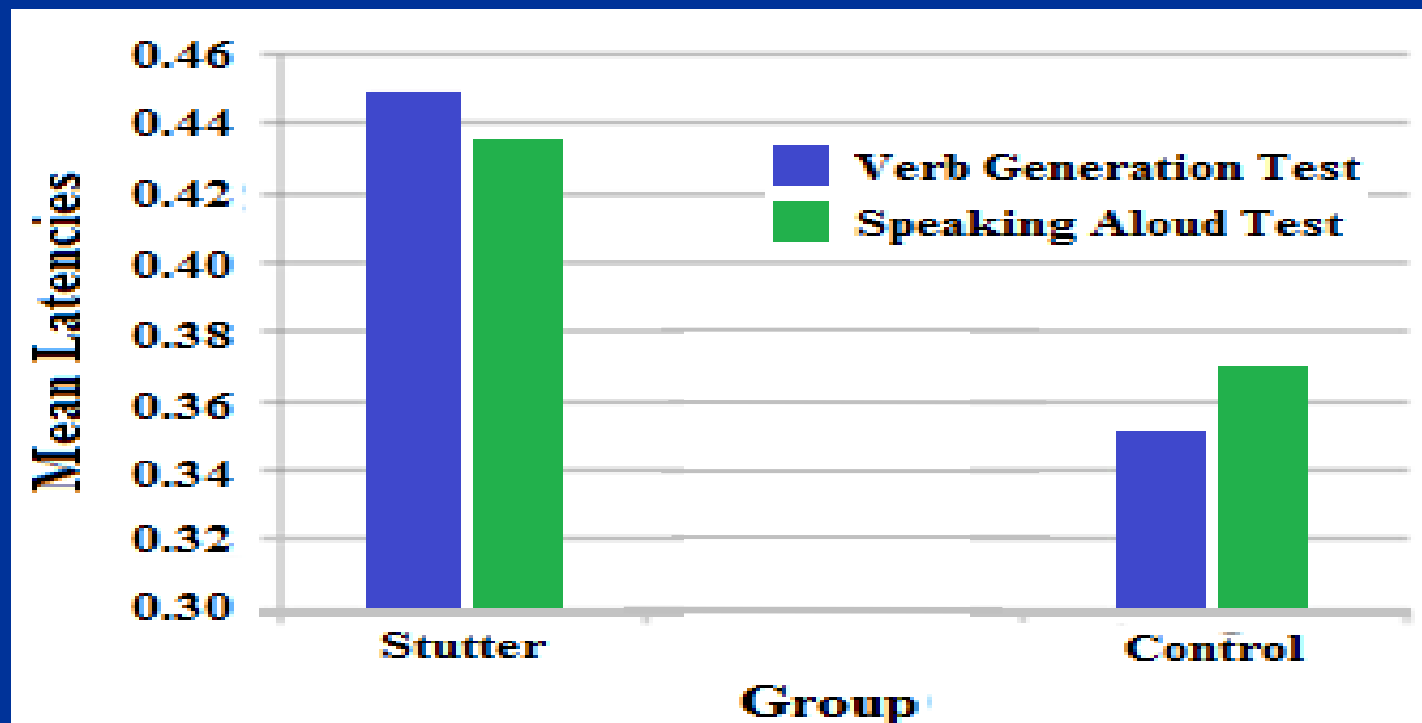
Trigger

148
MEG



Results Evoked reponses

- Statistically significant ($p\text{-value} < 0.0001$) delay in Broca's area activation in PWS compared to fluent speakers



Broca's area activation was significantly delayed in patients who stutter:

Table 1	Broca's Area Activity: Stutter vs. Fluent speakers				
Task	Group	N	95% CI	Mean Lat.	Test
Verb Generation	Stutter	9	0.427 to 0.470	0.448702	t-test $p < 0.0001$
	Control	4	0.322 to 0.379	0.3504	
Speaking Aloud (RA)	Stutter	10	0.414 to 0.453	0.433717	t-test $p < 0.0001$
	Control	4	0.342 to 0.415	0.37847	

Broca's Area during VG and SA language tests, Broca's Area activation was significantly delayed in patients who stutter in comparison to control subjects.

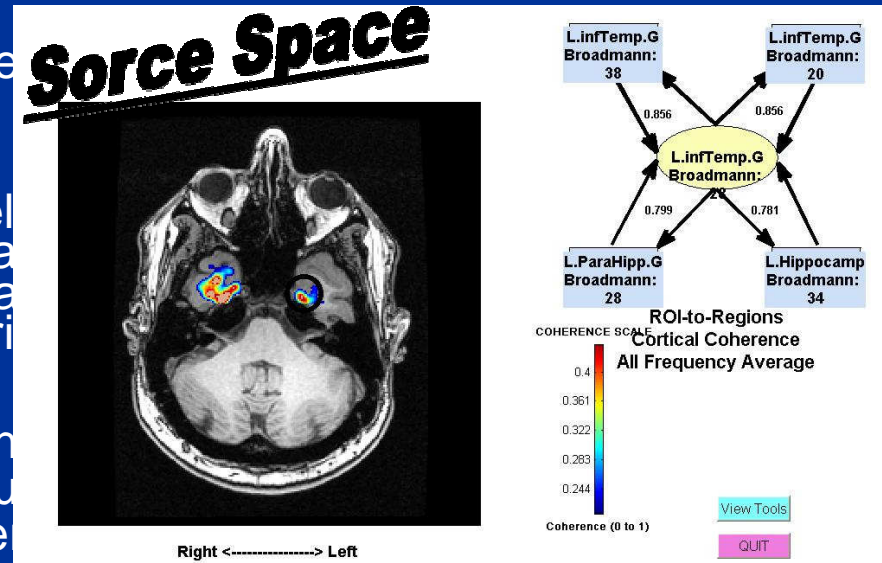
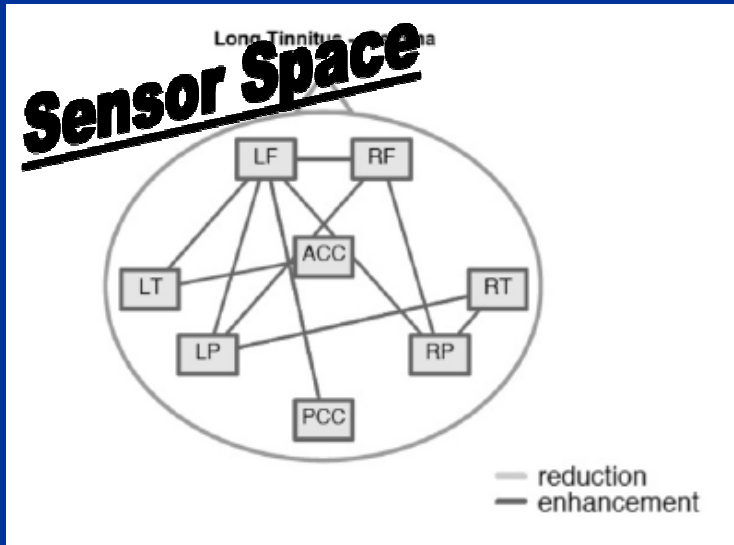
Results Functional Networks

Resting State

- Statistically significant ($p\text{-value} < 0.001$) difference in coherence levels between PWS and Fluent speakers were found in Broca's area
- Stuttering patient population had a mean coherence value that was 2 times greater than the mean coherence of the Fluent speaker population

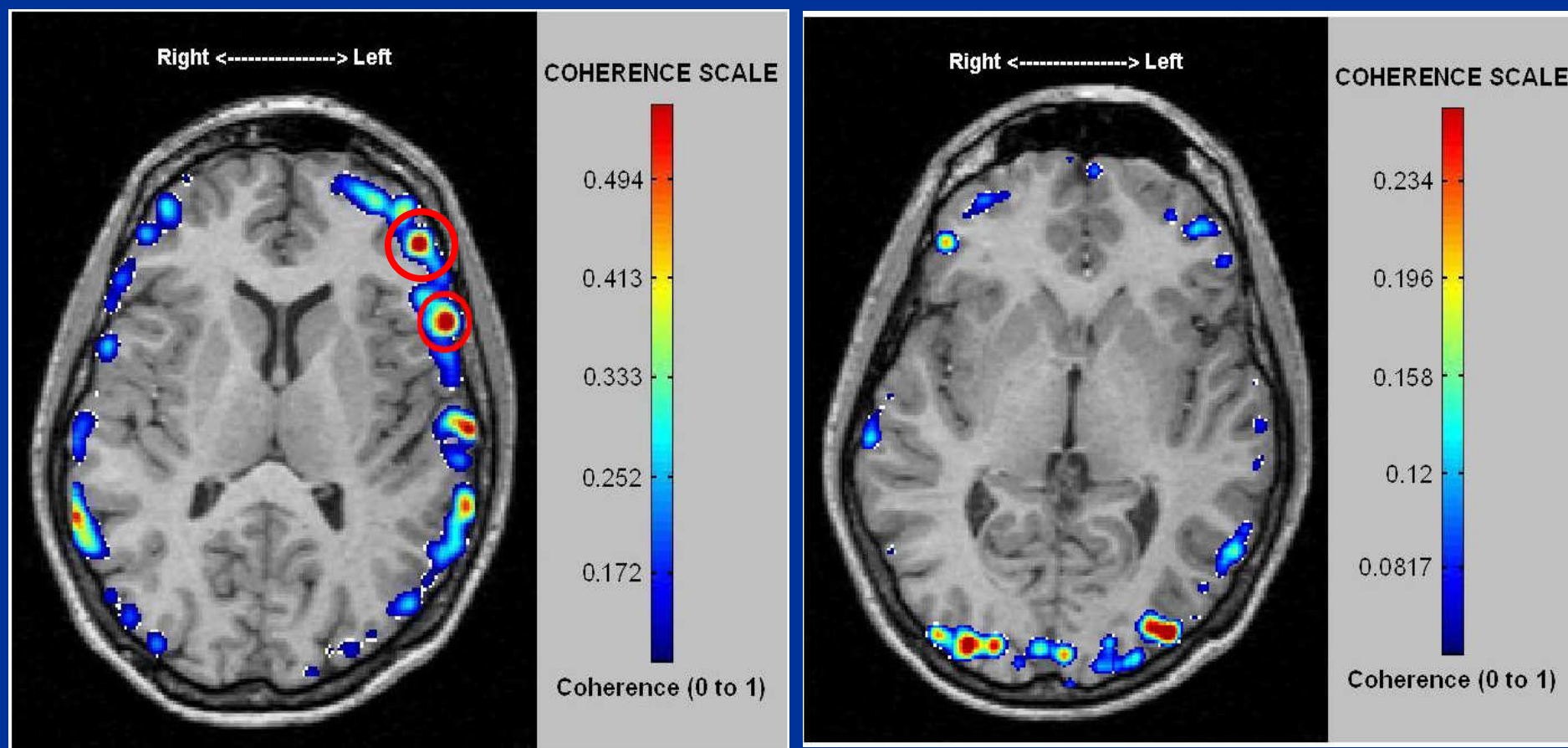
Coherence

- The analysis of coherence between EEG electrode site and MEG sensors has been performed for many years. However, at best only regional inference of cortical connectivity can be estimated without **first imaging brain activity**.



- Coherence reflects the degree of information flow between groups of neurons.
- Advanced network evaluation techniques (Granger causality, narrow band filtering or Essential Mode Decomposition with Hilbert transforms, wavelets) can be applied to non-stationary data.
 - Determine the direction of network interactions
 - Quantify significance of network structures

Significantly Higher Coherence in Patients Who Stutter



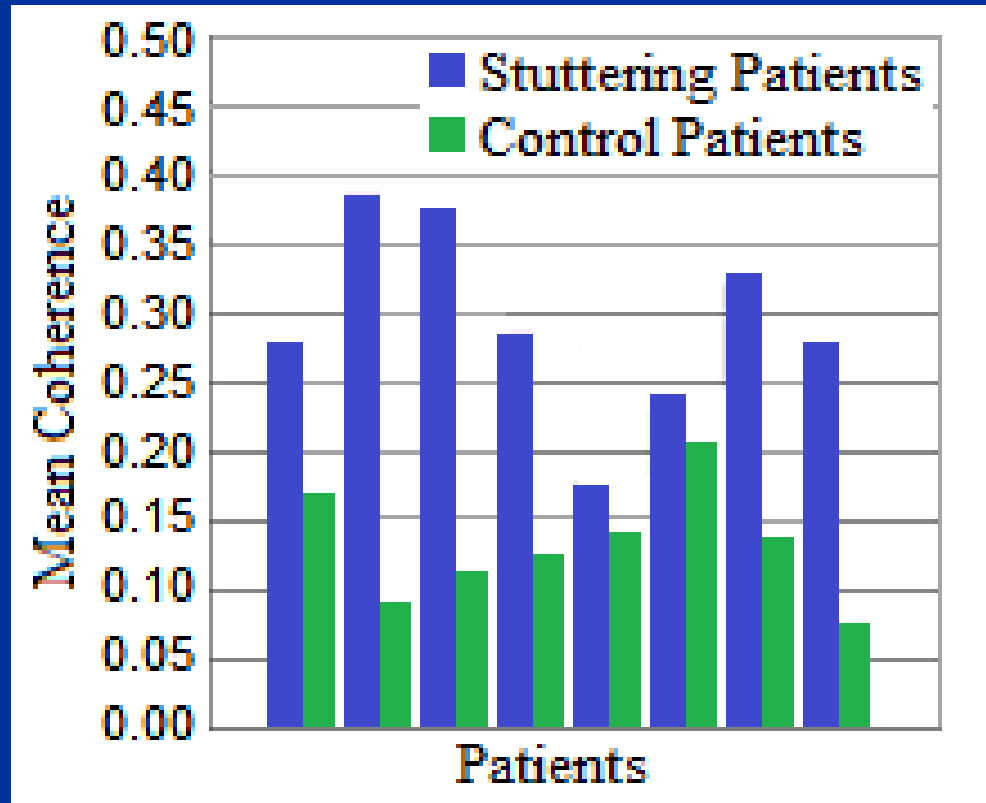
PWS had abnormal activity during resting state with greatest coherent activity in Broca's area. The fluent readers, on the other hand, showed little to no activity in the frontal lobe with greatest high coherent activity in the visual cortex.

Resting State Functional Brain Network Activity

Coherence Analysis: PWS vs. Fluent Speakers

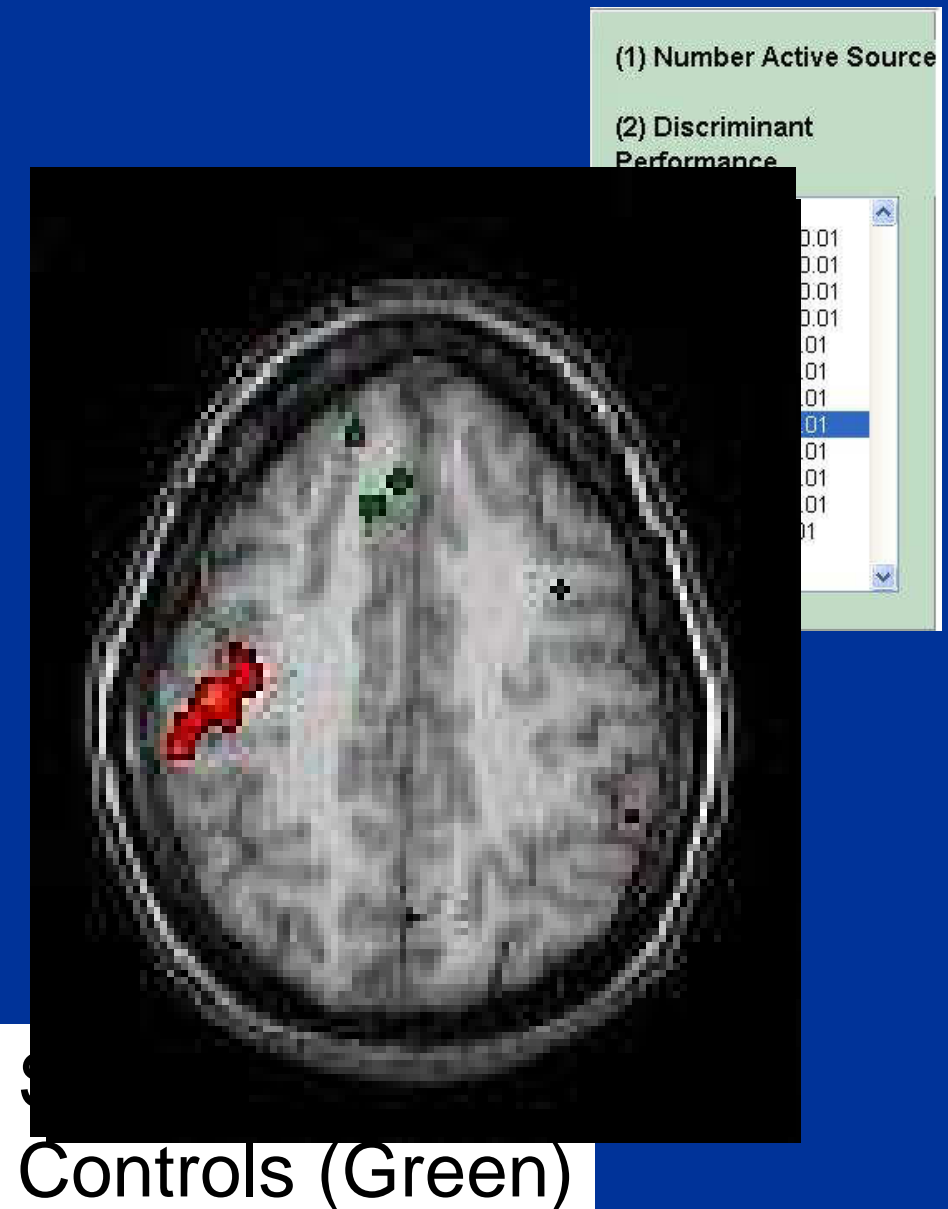
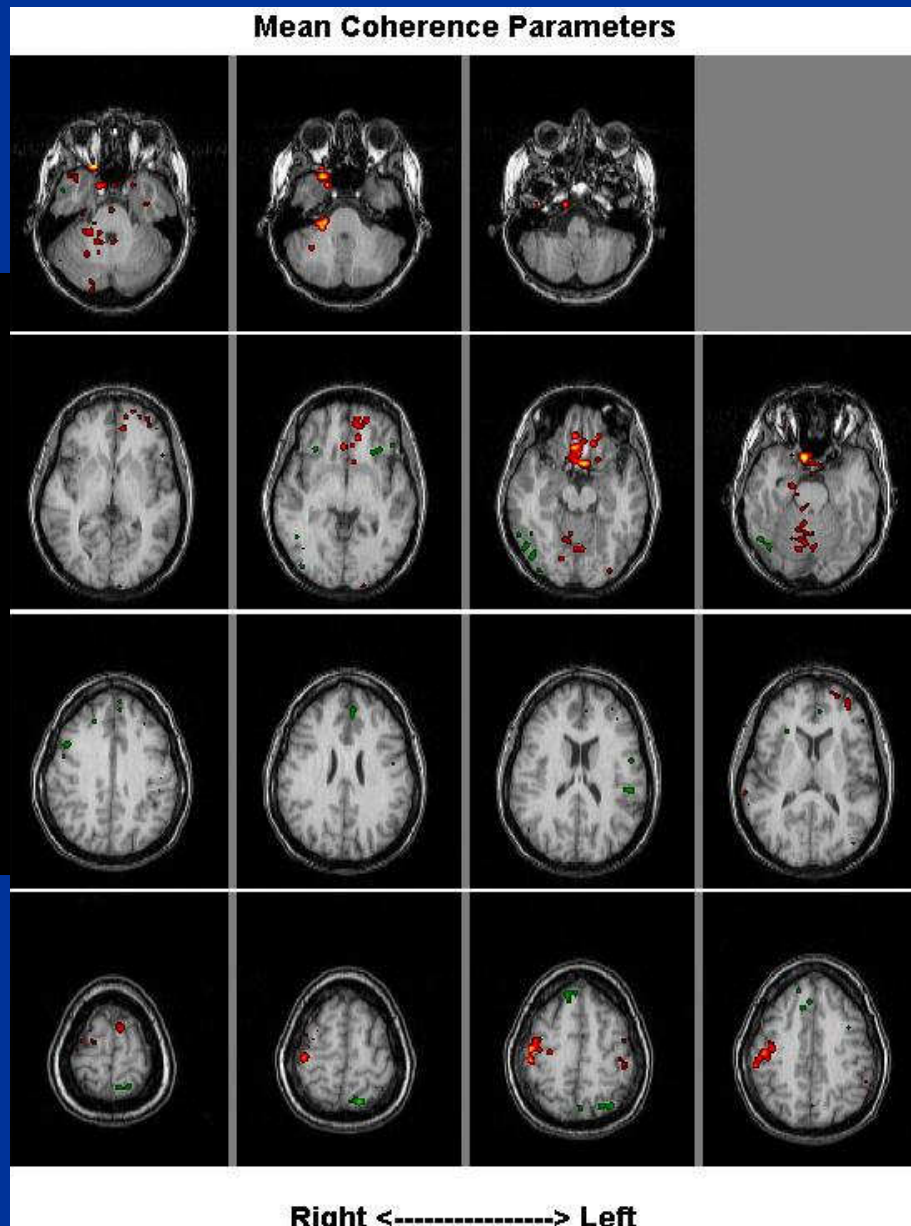
Group	N	95% CI	Mean Coh	Test
Stutter	9	0.247–0.373	0.309896	t-test $p < 0.0001$
Control	8	0.099–0.168	0.133358	

A paired t-test of Broca's area coherence levels during resting state of PWS vs. Fluent Speakers was statically different.



Mean coherences of PWS and Fluent Speakers indicates PWS had much higher mean coherences values in Broca's area during resting state compared to fluent readers..

Difference in Functional Coherent Resting Brain Activity 3-50Hz



Higher coherence levels in Broca's area During Rest... SO WHAT?

- If Broca's is already operating when not needed, it may not be as easily accessible when REALLY needed
- Activity needs to be re-directed, causing a minor delay that may result in difficulty initiating speech production
- Broca's area may then continue to function at a higher amplitude in turn causing the disfluencies experienced by PWS
- If this is the problem, HOW can it be fixed?

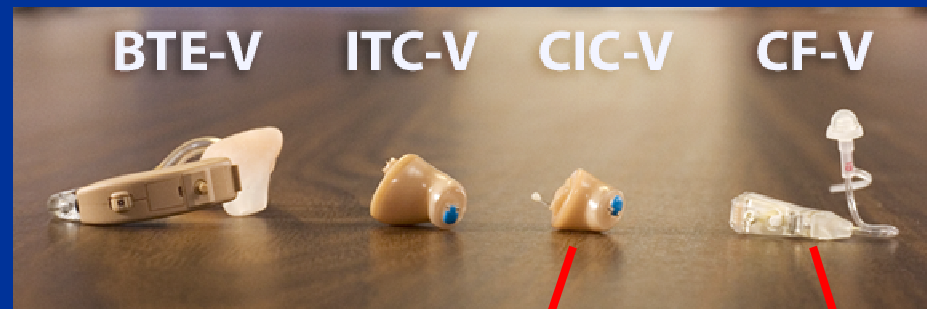
Treatment effects



- There are no cures for stuttering
- Pharmacological and clinical avenues for potential treatments are being pursued (Bothe 2006; Bothe 2006; Blomgren M. 2010; Ratner 2010).
- The nature of the treatment will differ, based upon a person's age, communication goals, and other factors.
- Therapy for stuttering is primarily done by a certified speech-language pathologist
 - The two therapy techniques most commonly used for pre-teens through adulthood focus on strategies for improved fluency (fluency enhancing techniques) and strategies for modifying the stutter (stuttering modification techniques).

Speech Easy®

- Altered Auditory Feedback (AAF)
- SpeechEasy® is an in-the-ear auditory feedback device that can enhance fluency in PWS.
- It combines delayed auditory feedback (DAF) with frequency altered feedback (FAF) to create a choral effect.
- The **choral effect** occurs when people who stutter speak or sing in unison with others, resulting in dramatically reducing or even eliminating the stutter.

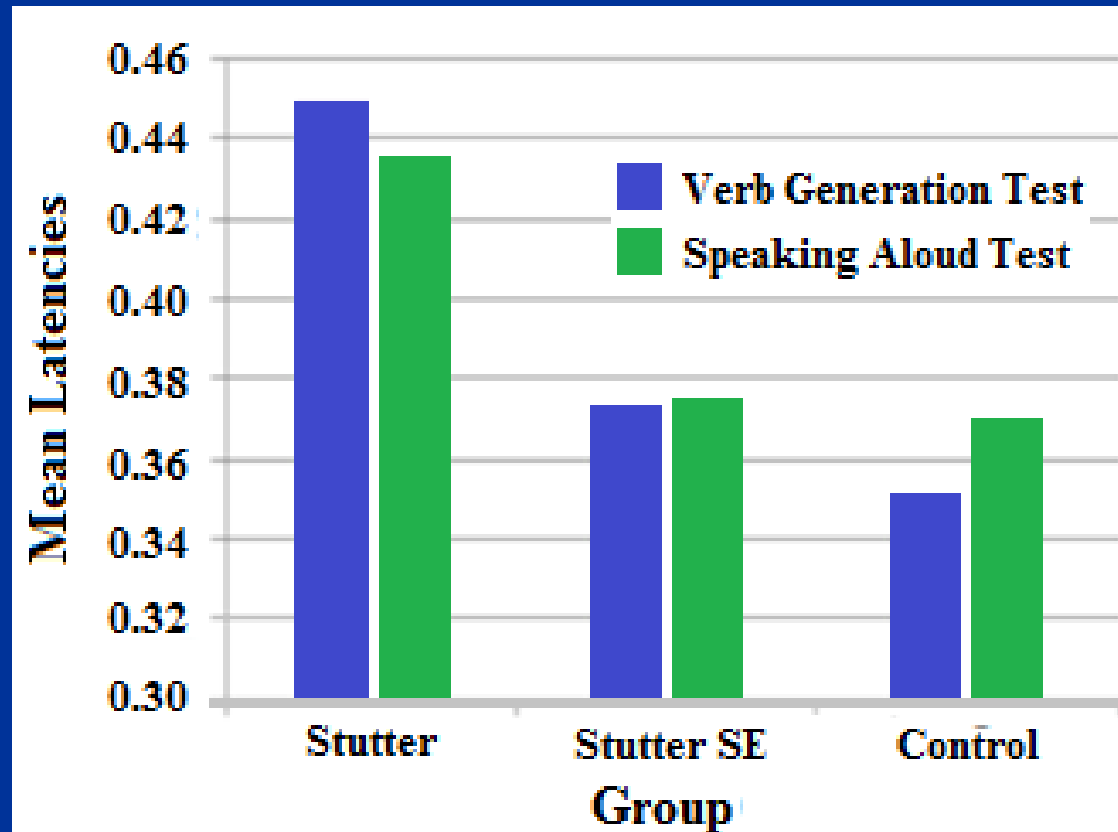


Results of Treatment on Evoked Brain activity

- We investigated the location of cortical processes of stuttering with and without the SpeechEasy® device
- Specifically latency and sequence of activation of the cognitive neural pathways involved in stuttering
- Both the overt verb generation (VG) and reading aloud (RA) task, activation in Wernicke's area were similarly active regardless of the use of the SpeechEasy® device
 - with VG:250+16ms; RA:247+ 07ms
 - without VG:249+25ms; RA:245+15ms

Results of Treatment on Evoked Brain activity

- Broca's area activation was significantly delayed in PWS (434+20ms) compared to Fluent speakers (378+36ms) [$p < 0.0001$] during reading aloud
- Treatment effects of the SpeechEasy® device normalized the latency of Broca's activation in PWS (375+22ms) to the point that no statistically significant comparison could be achieved with fluent speakers [$p < 0.05$].
- This same normalization of the latency was found in the overt verb generation task where PWS also had delayed Broca's activation (450 + 22ms) compared to normal fluent readers.



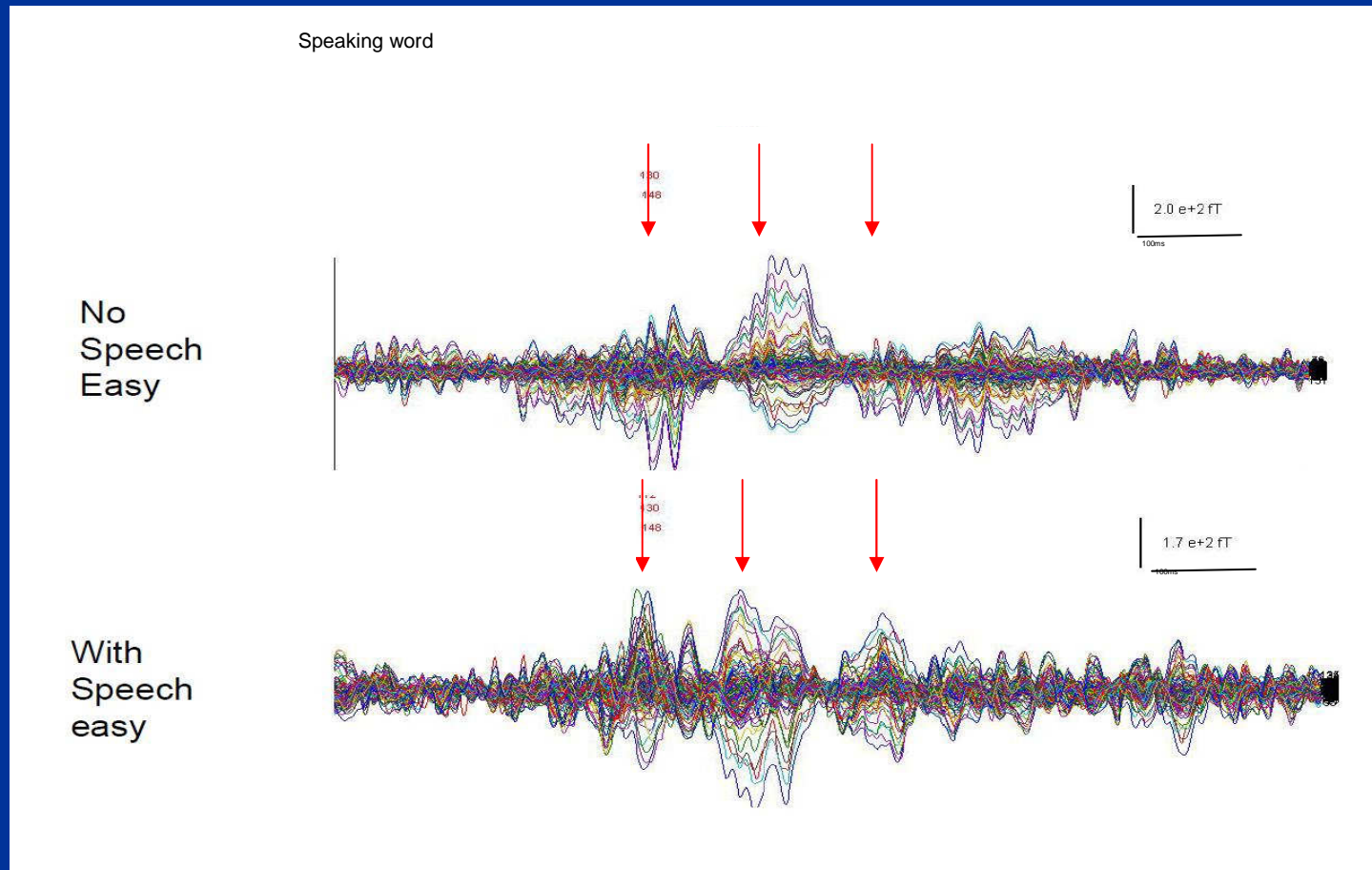
The use of SpeechEasy

significantly normalized Broca's area activity in PWS:

Table 2	Broca's Area Activity: Use of SpeechEasy				
Task	Group	N	95% CI	Mean Lat.	Test
Verb Generation	Stutter SE	9	0.347 to 0.398	0.372679	t-test $p < 0.0001$
	Stutter	9	0.427 to 0.470	0.448702	
Speaking Aloud (RA)	Stutter SE	10	0.353 to 0.397	0.374733	t-test $p < 0.0001$
	Stutter	10	0.414 to 0.453	0.433717	
Verb Generation	Stutter SE	9	0.347 to 0.398	0.372679	t-test $p = 0.244$
	Control	4	0.322 to 0.379	0.3504	
Speaking Aloud (RA)	Stutter SE	10	0.353 to 0.397	0.374733	t-test $p = 0.832$
	Control	4	0.342 to 0.415	0.37847	

PWS with SpeechEasy showed statistically significant decreases in Broca's area activation latency compared to PWS without the fluency aid. SpeechEasy normalized the latency of Broca's area activation such that the comparison between PWS with SpeechEasy and fluent speakers was not statistically significant.

MEG Waveforms

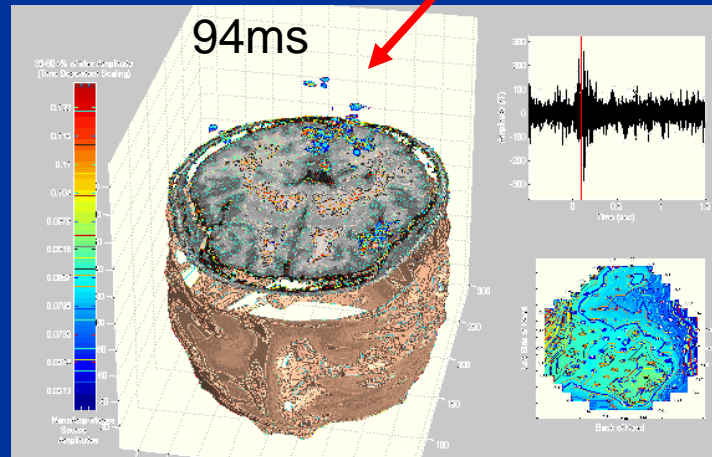


148 MEG channel butterfly plots. MEG averaged evoked responses during speaking words aloud. Initial peak is visual processing, second peak is Wernicke's activation, and third peak is Broca's activation. Note in bottom trace Broca's activation is clearly seen with the use of the SpeechEasy device.

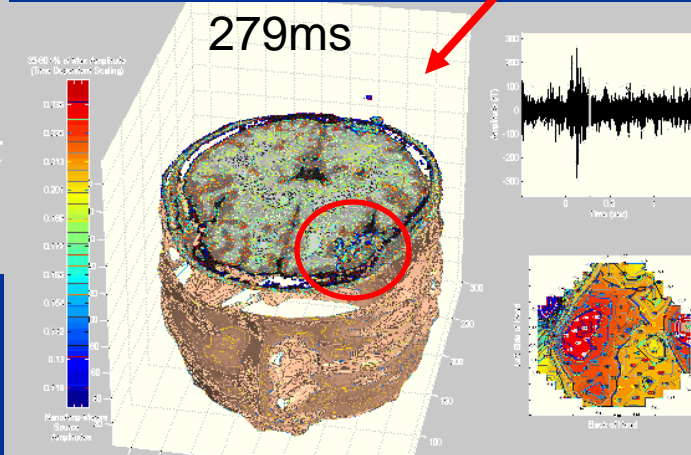
PWS Reading aloud

AWS reading aloud

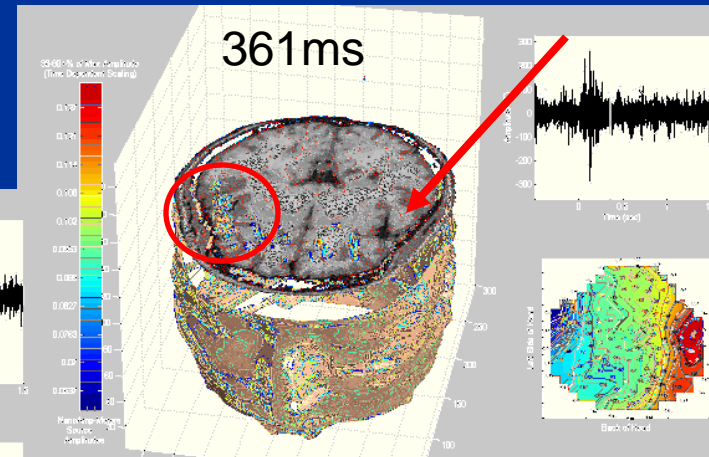
94ms



279ms



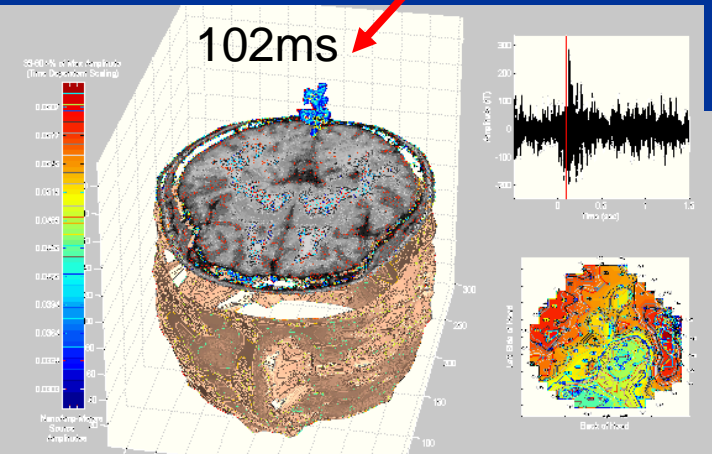
361ms



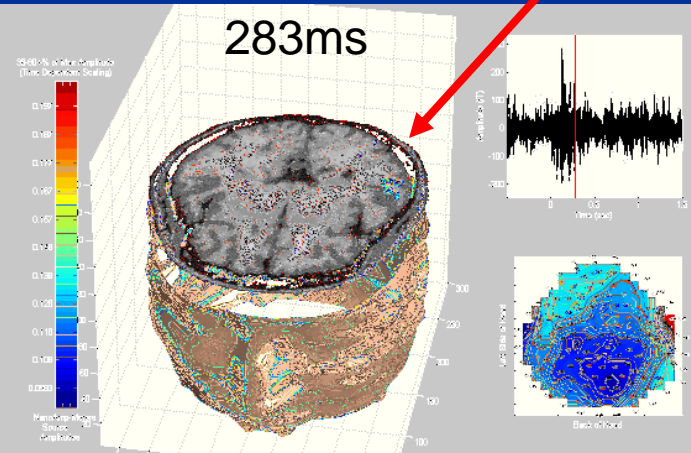
**NOTE:
Visual
Wernicke's
Broca's**

**AWS reading aloud
with the Speech Easy device in place**

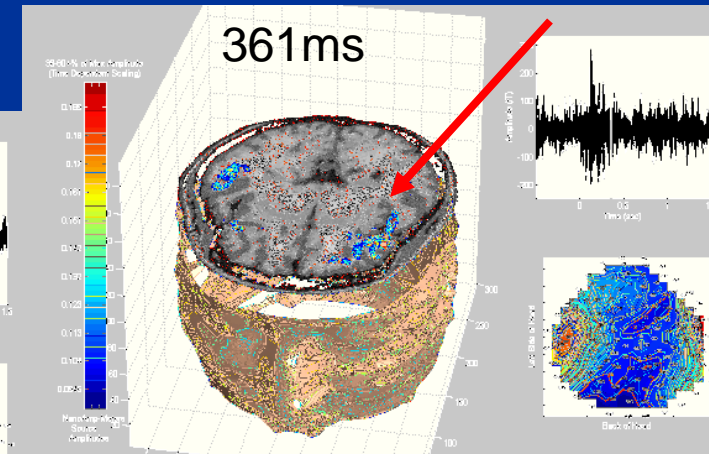
102ms



283ms



361ms



Conclusion

- Cortical areas of high coherent activity in the inferior frontal gyrus and motor cortex during the resting state were seen in PWS, when not speaking.
- These data showed an abnormal functional resting state network of PWS compared to fluent reading control subjects.
- Looking at the combination of the resting state data and the evoked data, it appears that PWS may have a defect in the cortical activation of Broca's area.
- Therefore, it is thought that when PWS need to access these areas, they are more difficult to access because these cortical areas are already being activated (during the resting state) and they need to redirect networks to accomplish a task.
- Without the SpeechEasy®, there was no clear peak in Broca's area, indicating low levels of activation. When the SpeechEasy® was being used, there was a clear peak, showing higher levels of activation.
- We hypothesized that when the SpeechEasy® is utilized, it may disrupt the resting state functional network, creating the ability to more effectively activate Broca's area for motor speech thereby creating improved fluency.

Implications/Future Research

- Brain imaging studies with PET, fMRI, and MEG have indicated that there are connectivity differences in the left inferior frontal, Auditory and premotor cortices in PWS.
- The deficiencies in these communicating brain regions hinder the efficient planning and execution of sound production.
- The fine spatial and temporal resolution of MEG makes it possible to study brain activation differences that are undetectable with other imaging techniques
- Research performed on children close to the onset of stuttering could provide answers to how the speech processing network differs from those children who do not stutter. This would lead to an understanding of how remediation could change the stuttering brain networks.
- Currently researchers are working to help speech-language pathologists determine which children are most likely to outgrow their stuttering and which children are at risk for continuing to stutter into adulthood.
- Advances in the study of the underlying neuronal bases for stuttering may lead to an objective biological marker for clinicians to identify these two groups.

Thank you for your attention!

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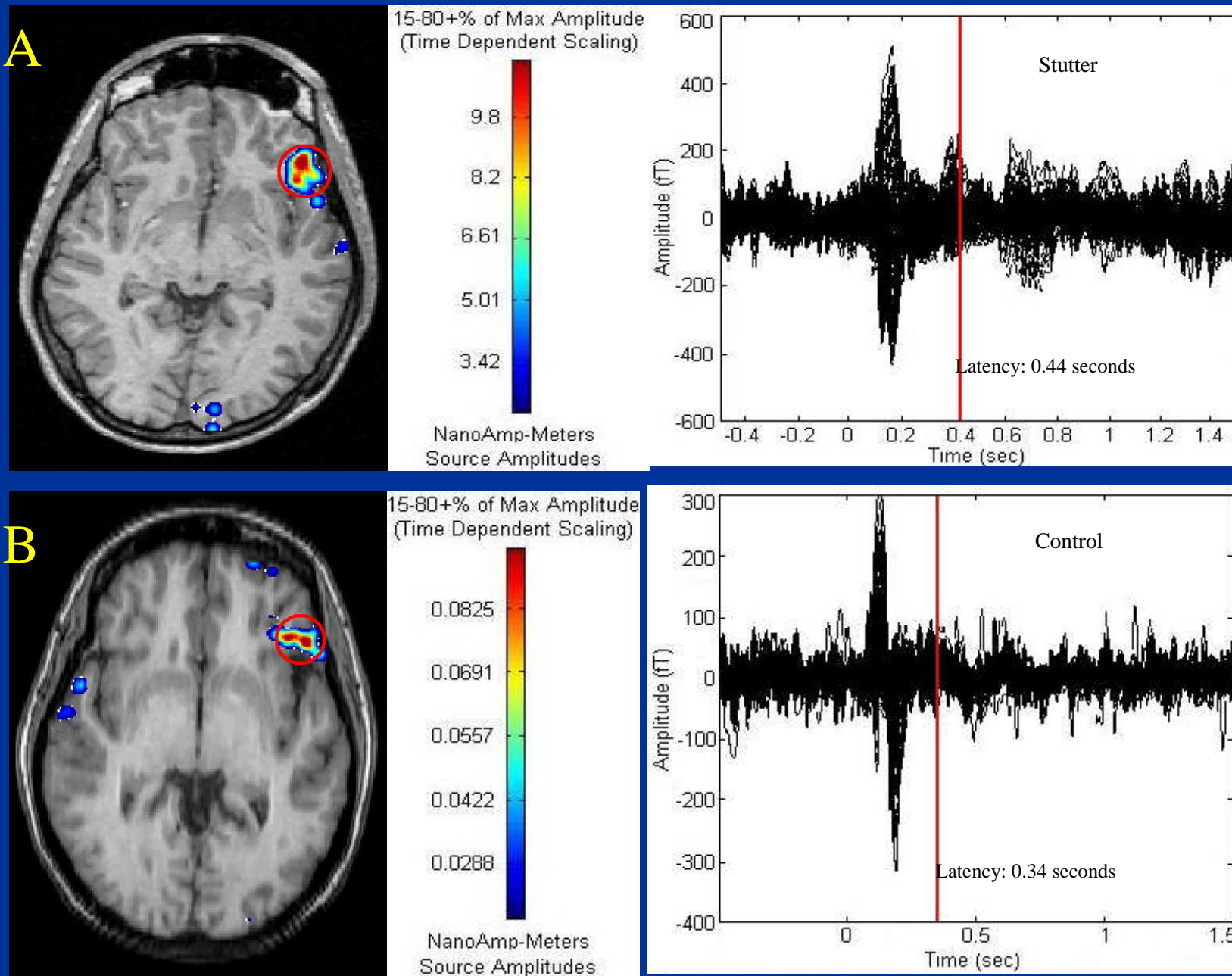
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Margaret Greenwald, PhD
Li Hsieh, PhD



MR-FOCUSS/Minimum Norm

- A non-linear current distribution imaging technique
- Images extended and compact sources of neuronal activity
- Incorporate a wavelet basis to obtain a multi-resolution description of the cortical source structure
- Performs focal changes of the source structure amplitudes for enhanced imaging of multiple simultaneously active compact sources
- For statistical robustness, ~20 solutions averaged for image
- Relatively insensitive to noise
- Useful for studying the sequence of interhemispheric neuronal activity
- Can study time evolution of sources

Activation Amplitude and Timing During Verb Generation



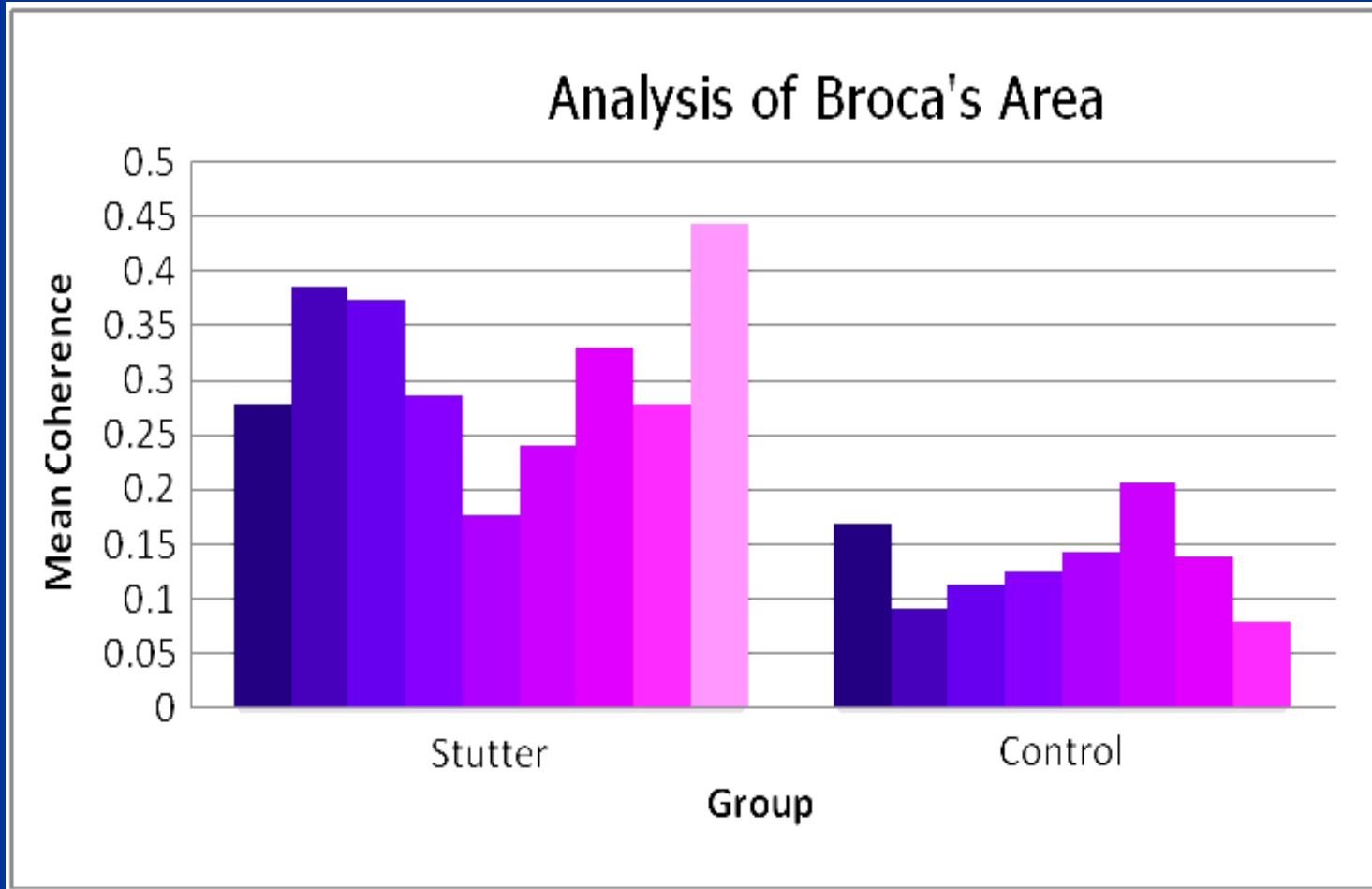
A: Stuttering Subject:
Latency = 440 ms

B: Control Subject:
Latency = 336ms

Noticeably later
Broca's activation
In the Stuttering
Subject

Higher amplitude
of Broca's
Activation in the
Stuttering Subject

Coherence Values



Mean coherence was 2 times greater in PWS than in the control subject population