Stuttering Research

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Haskins Laboratories

Stuttering

- Developmental disorder occurs in 5% of children
- Spontaneous remission in approximately 70% of cases
- Approximately 1% of adults with persistent stuttering
- Neither etiology nor pathogenesis is known
- Majority of research is in adults
- Some evidence suggests differences in children

Challenges in Stuttering Research

- Multifactorial
- Behavioral symptoms
- Language symptoms
- Neural symptoms
- Genetic component
- Experiential component
- Cognitive and emotional components

Some general methods for investigating stuttering

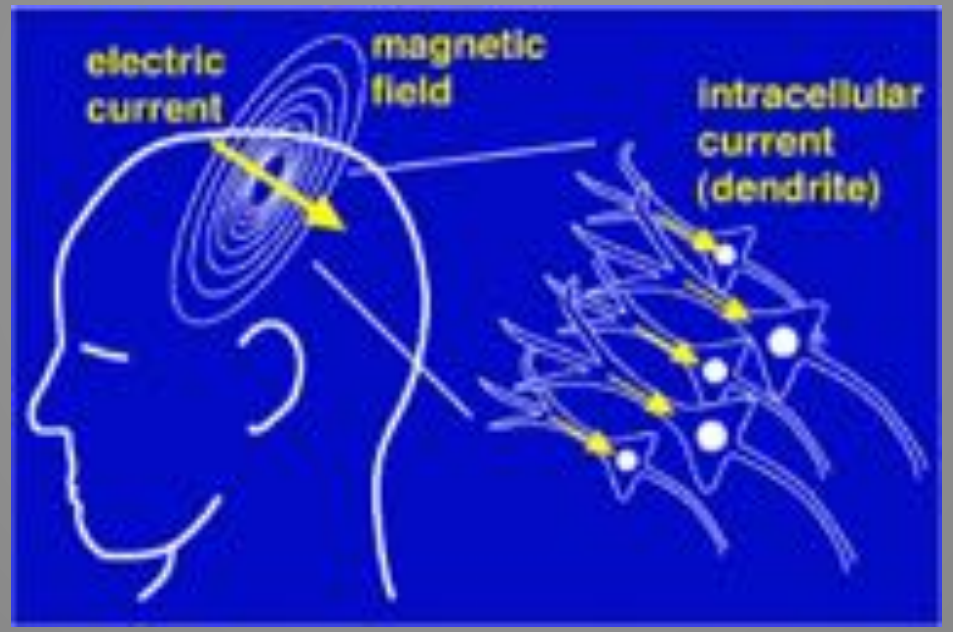
- Nonhuman studies
  - A Mutation Associated with Stuttering Alters Mouse Pup Ultrasonic Vocalizations
- Human genetics
- Behavioral approaches
- Instrumental approaches
  - Speech production and perception
- Neuroimaging
  - MEG/EEG
  - PET/MRI/fMRI—structure; function
  - Neurochemistry
- Complementary ways to evaluate brain, behavior and the relationship

Speech production differences in individuals who stutter

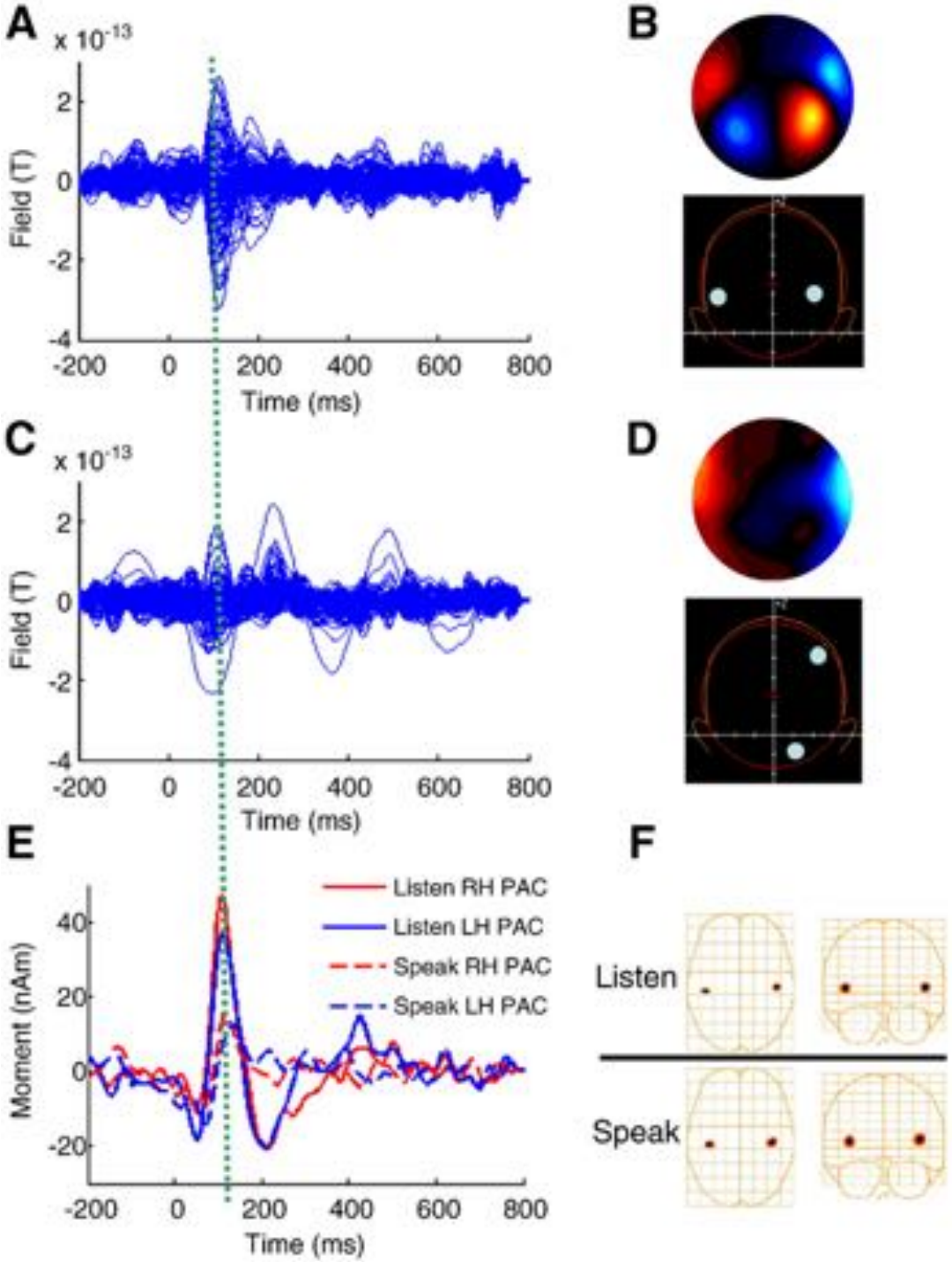
- Reaction time differences
  - Slower initiating speech
- Acoustic differences
  - Longer durations, slower speaking rate and consonant-vowel transitions
- Movement differences
  - Generally longer durations, slower movements, movement sequencing
- Differential response to auditory feedback
  - Delayed auditory feedback

Auditory processing and speech production

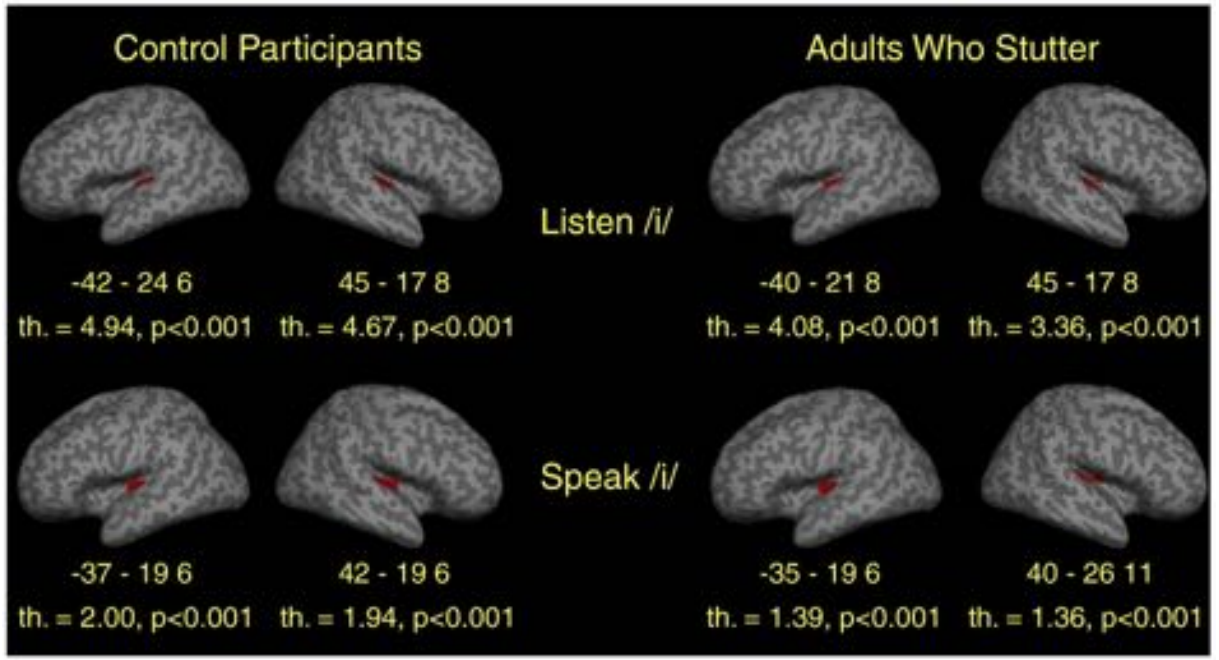
- **Magnetoencephalography** (MEG) is a functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using very sensitive magnetometers.



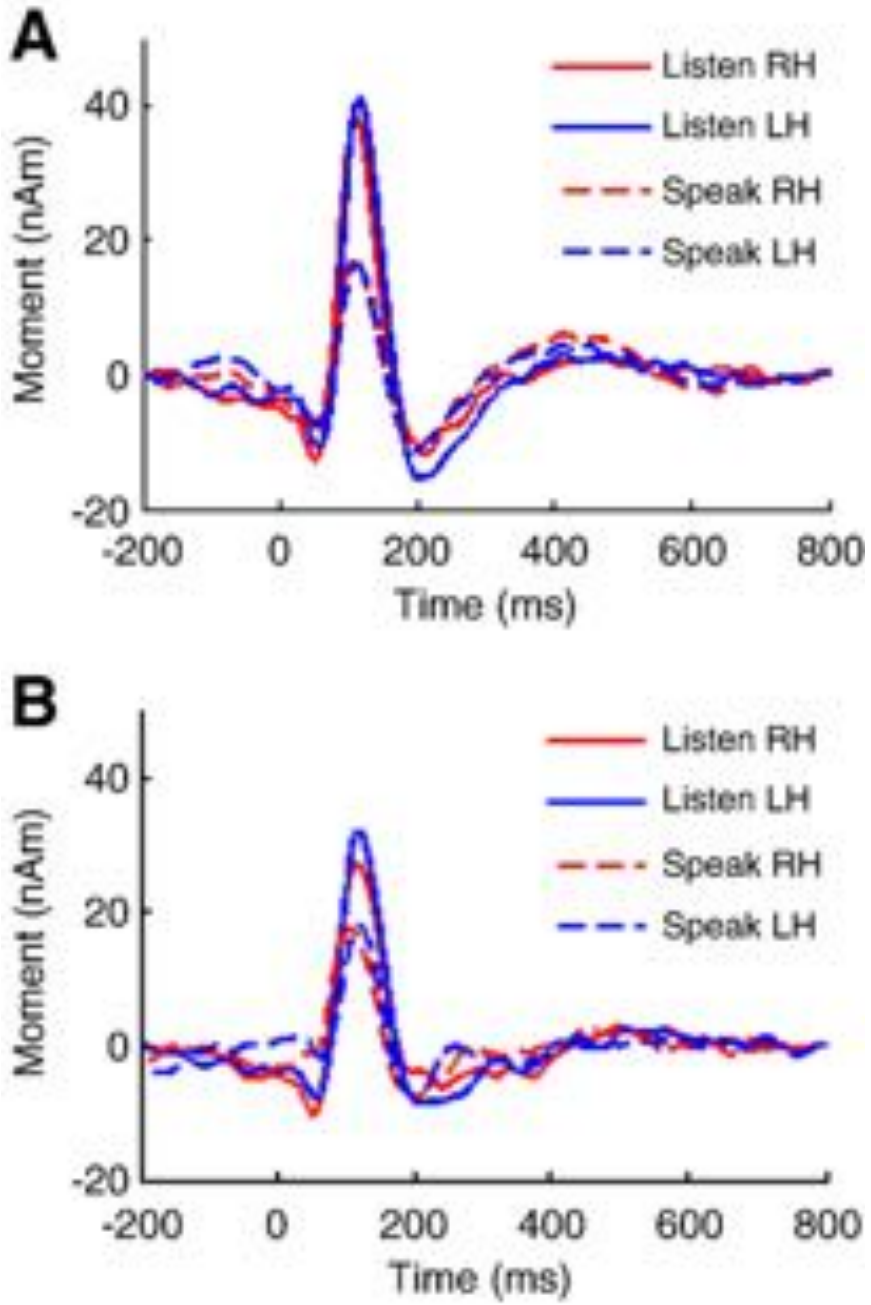
The MEG (and EEG) signals derive from the net effect of ionic currents flowing in the dendrites of neurons during synaptic transmission.



Adults who stutter--Listening to a 1 kHz tone, produced words and listened to playback of their own production of words.

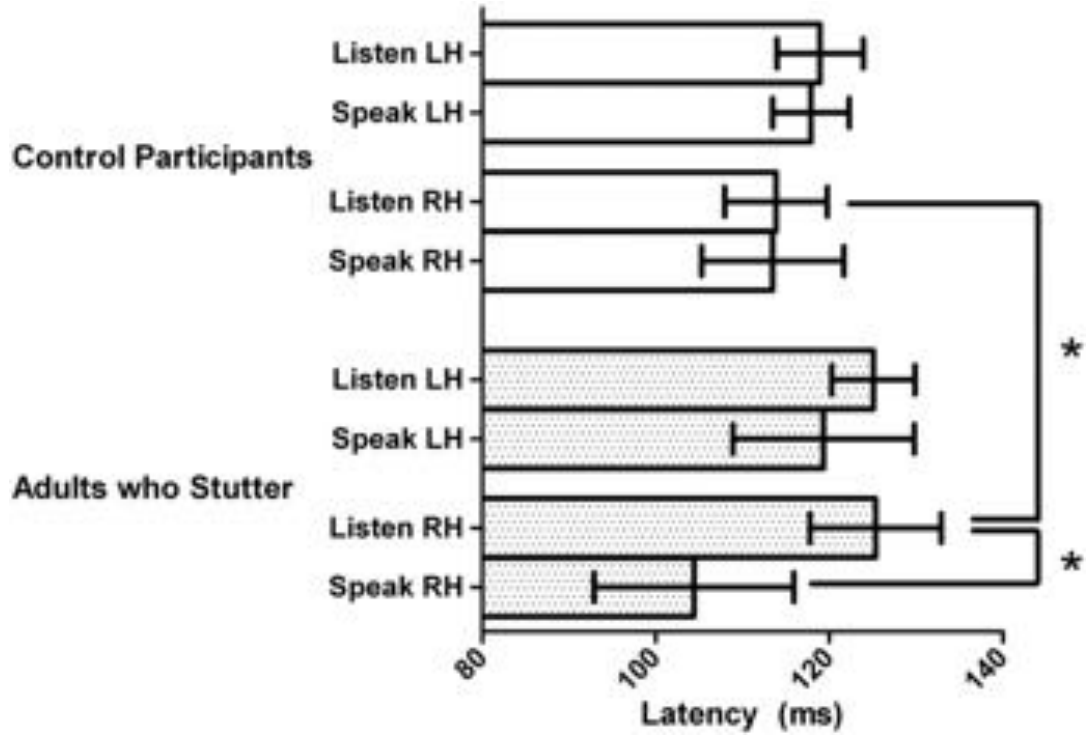


Beal et al., 2010 NeuroImage Auditory evoked fields to vocalization during passive listening and active generation in adults who stutter.



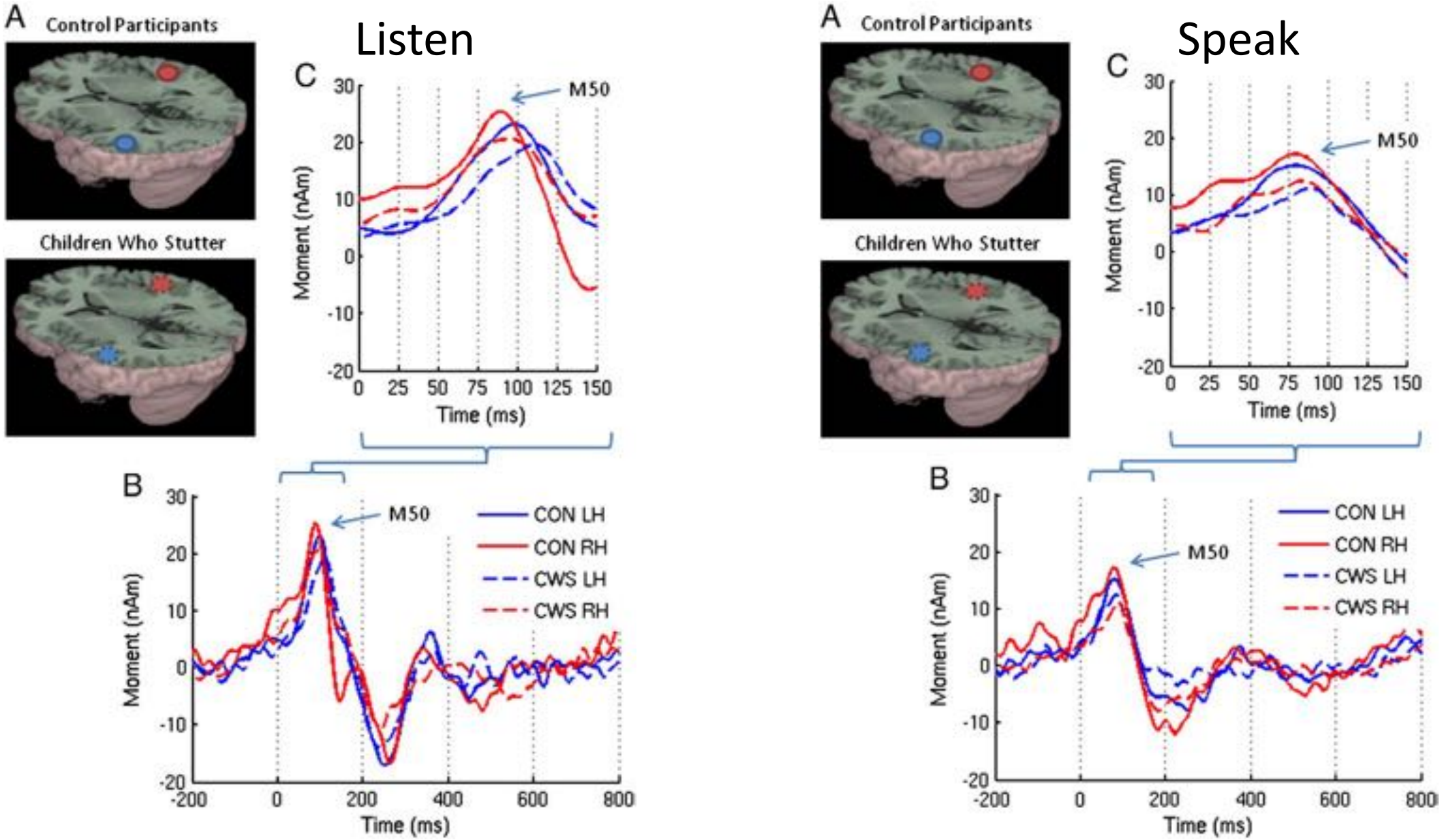
Control

AWS



There are timing, rather than amplitude, differences in auditory processing during speech in adults who stutter.

Children who stutter--Listening to a 1 kHz tone, produced words and listened to playback of their own production of words.



Beal et al. (2011) NeuroImage Speech-induced suppression of evoked auditory fields in children who stutter.

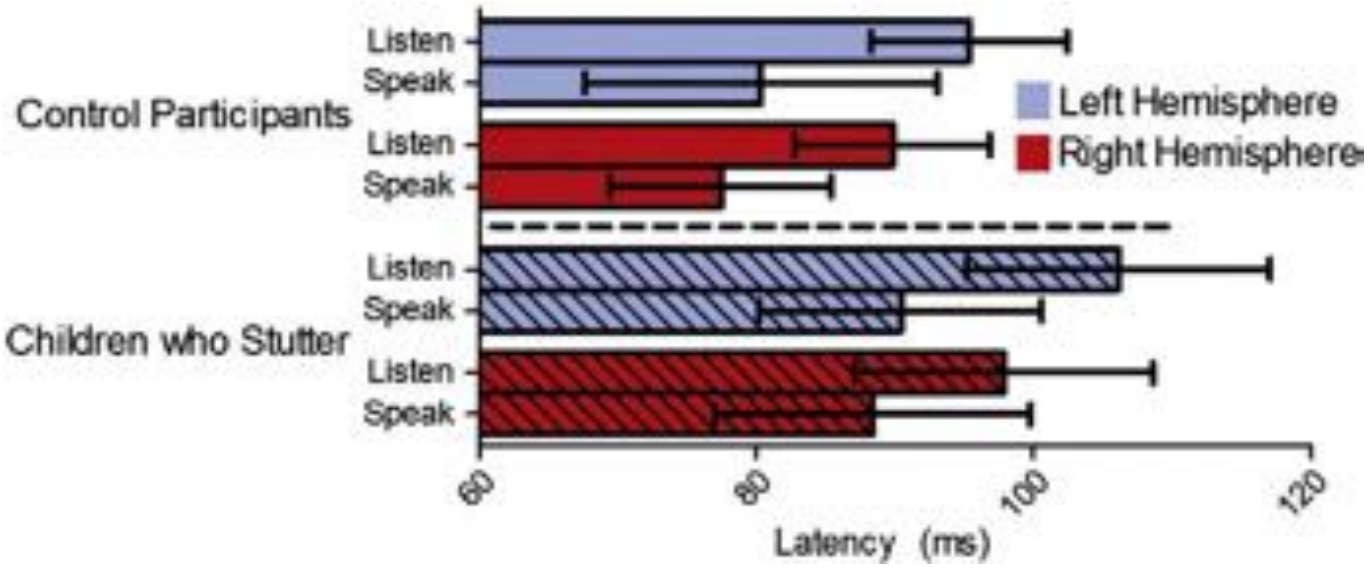


Fig. 7. The results of the listen and speak vowel task latency analysis. The children who stutter had delayed M50 peak latencies for the listen vowel and speak vowel tasks relative to the control participants.

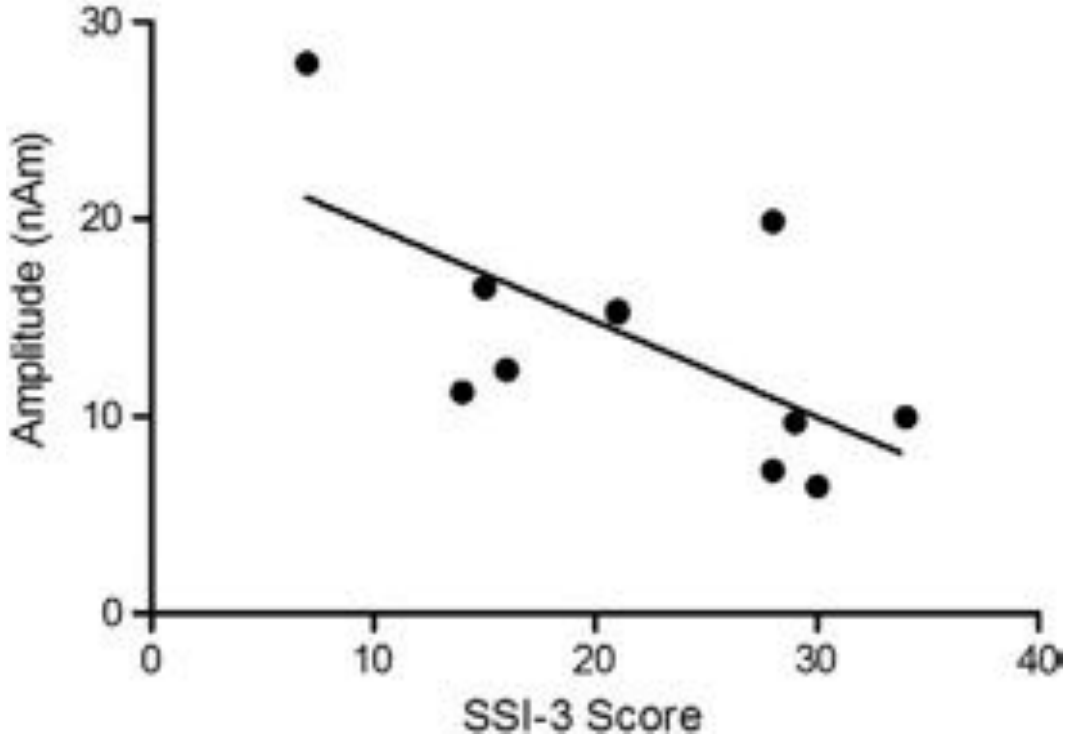
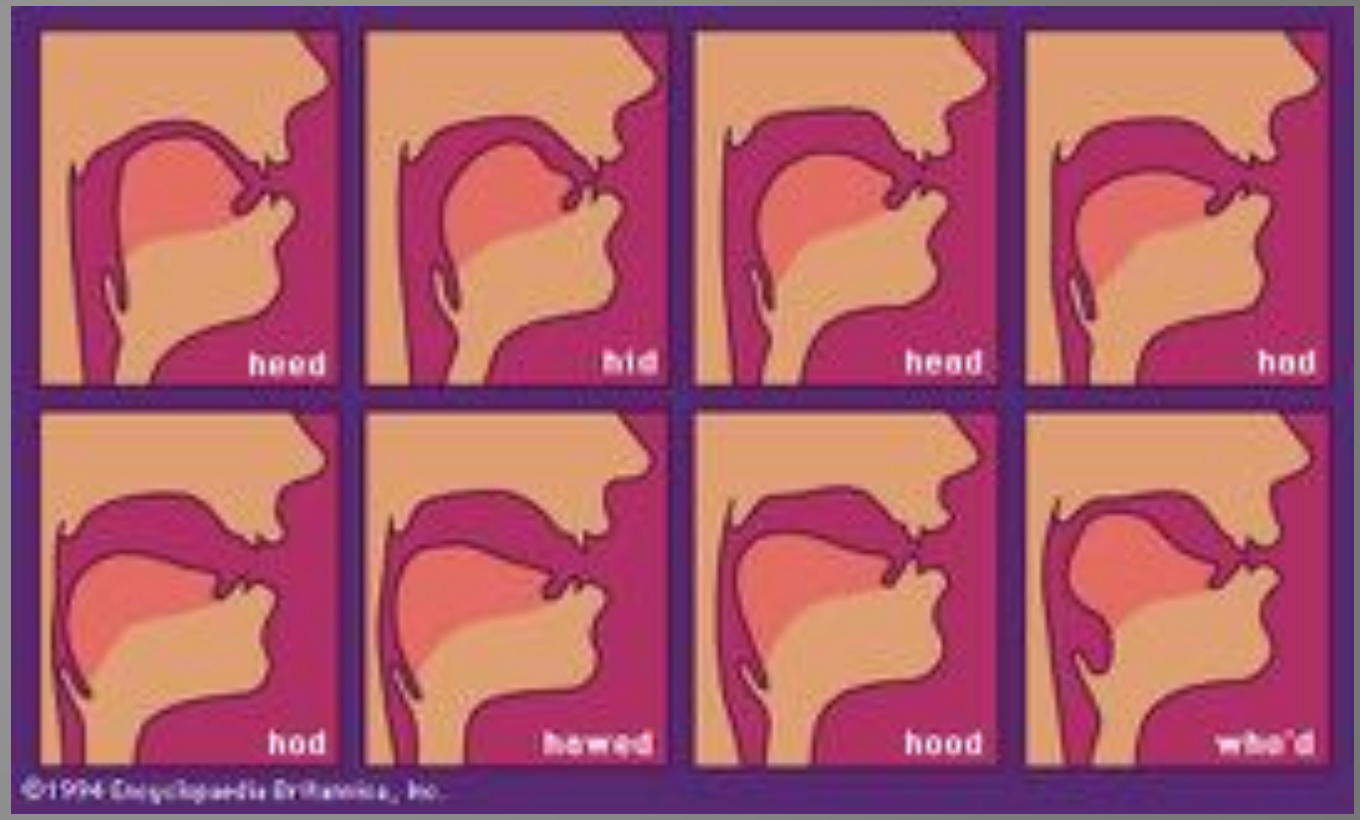


Fig. 6. For children who stutter, left hemisphere amplitude for the speak task had a negative correlation with stuttering severity as measured with the SSI-3.

Auditory feedback manipulation

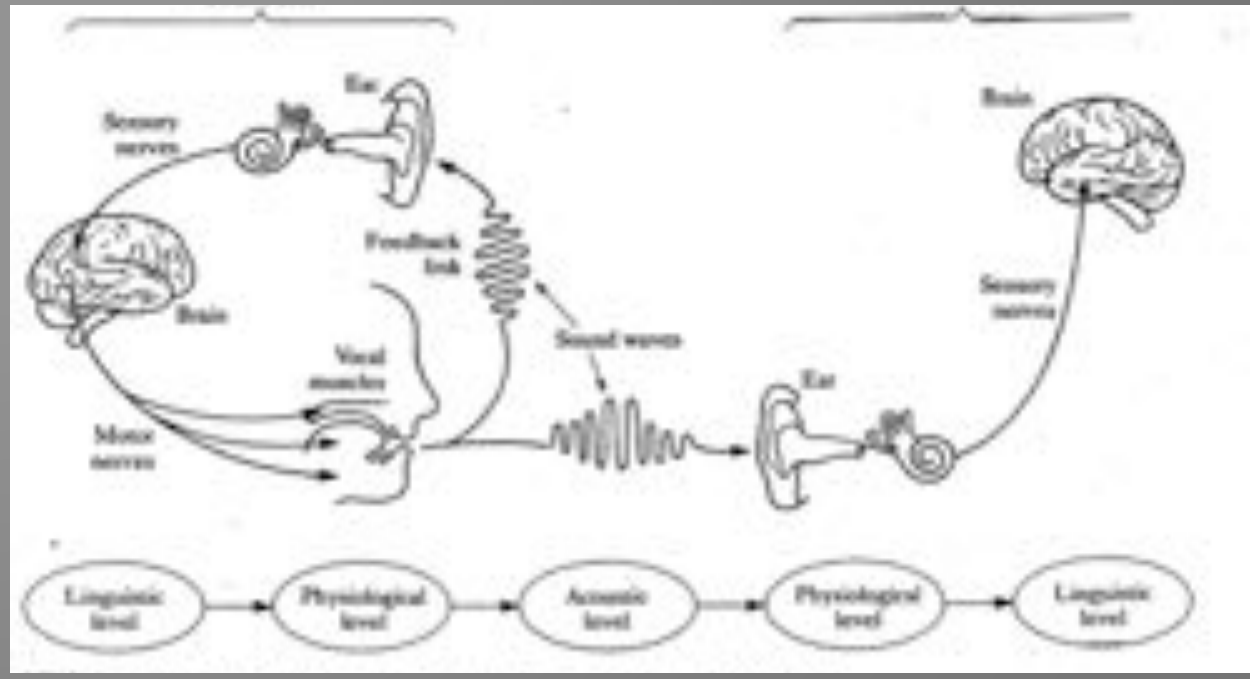
- Real-time signal processing to manipulate of acoustic-phonetic features during speech production to create a mismatch between what is produced and what is heard
- Modify voice pitch (laryngeal vibration) and/or formant structure (position of the tongue in the mouth-speech movement)
- Unpredictable and intermittent (control) or constant and predictable (learning)



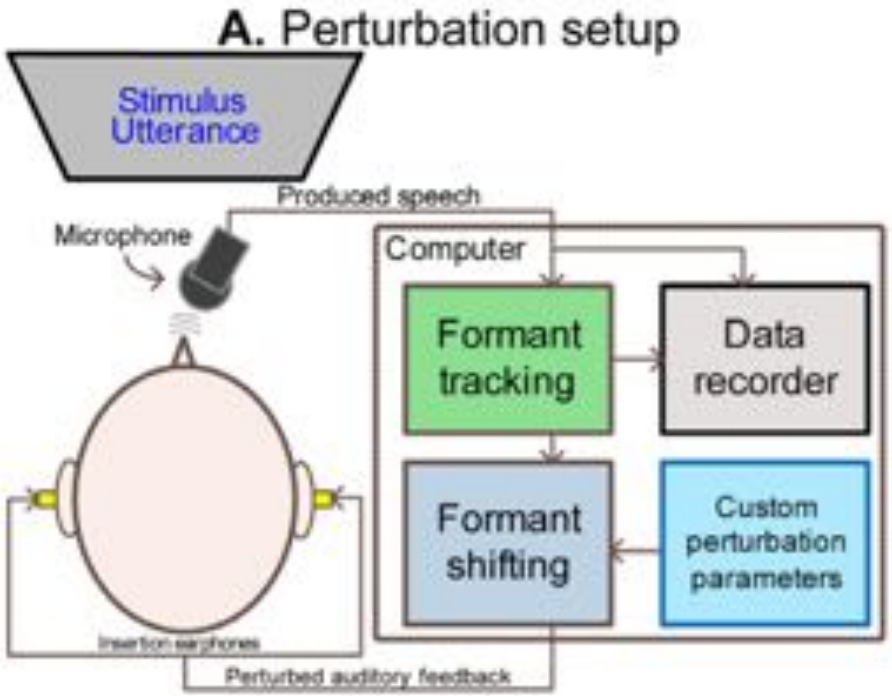
Sensorimotor integration

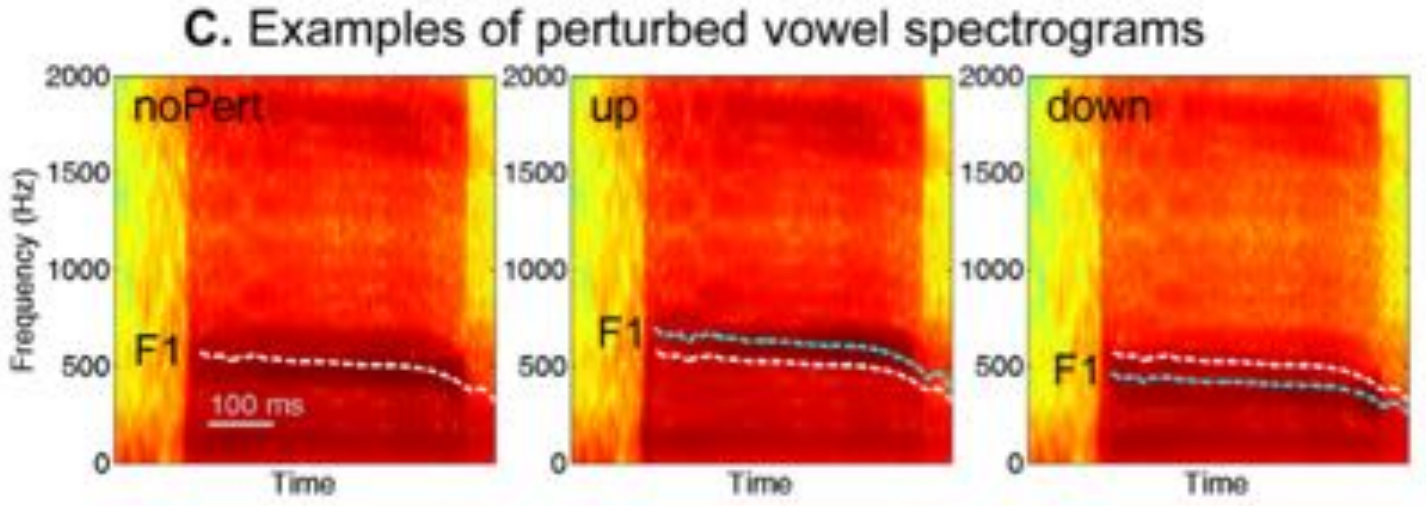
External feedback (exafference) comes from outside the body with information on requirements, performance/results

Internal feedback (reafference)—comes from the performer, from the body and it is self-generated

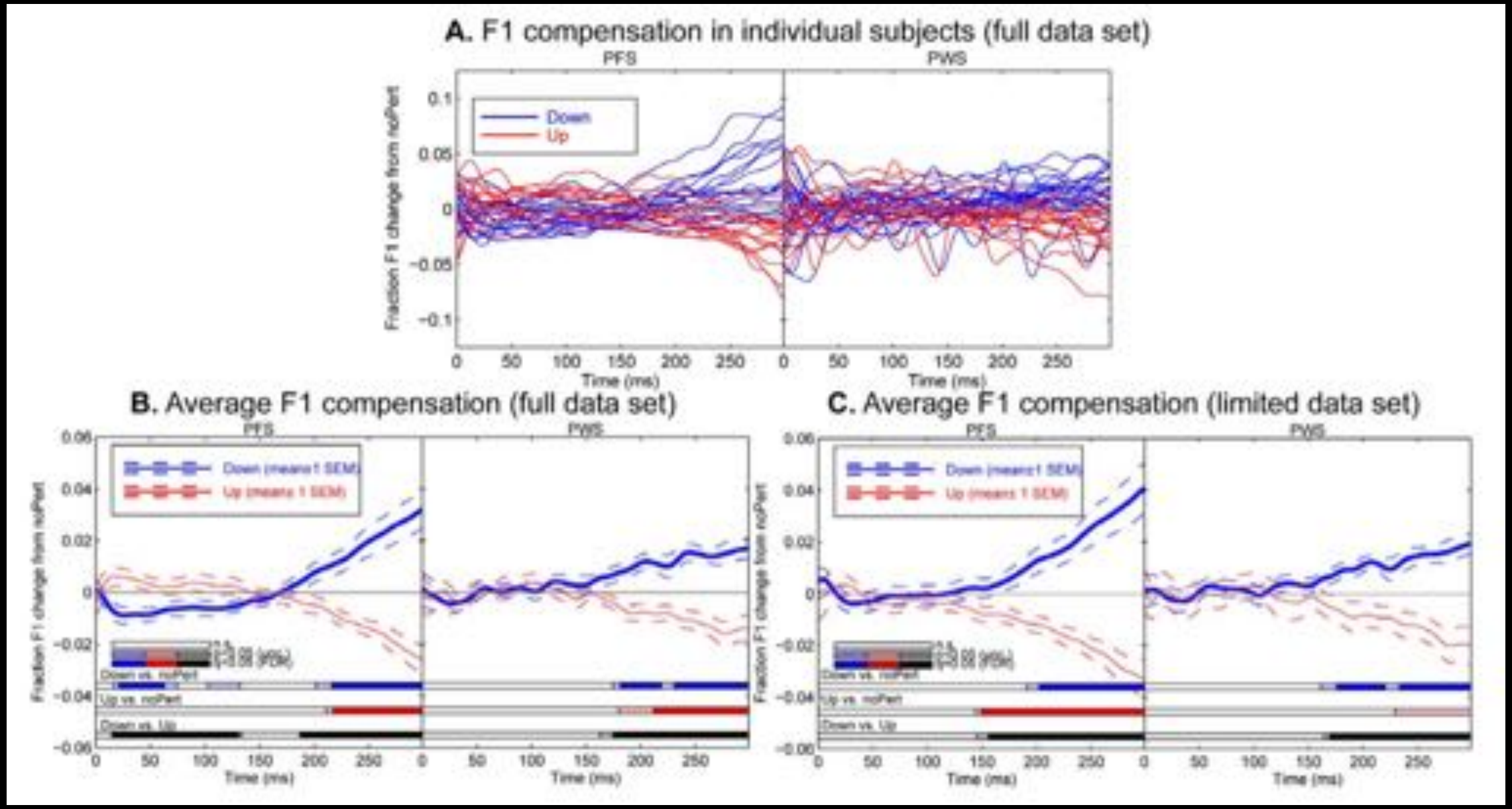


Auditory feedback-formant perturbation

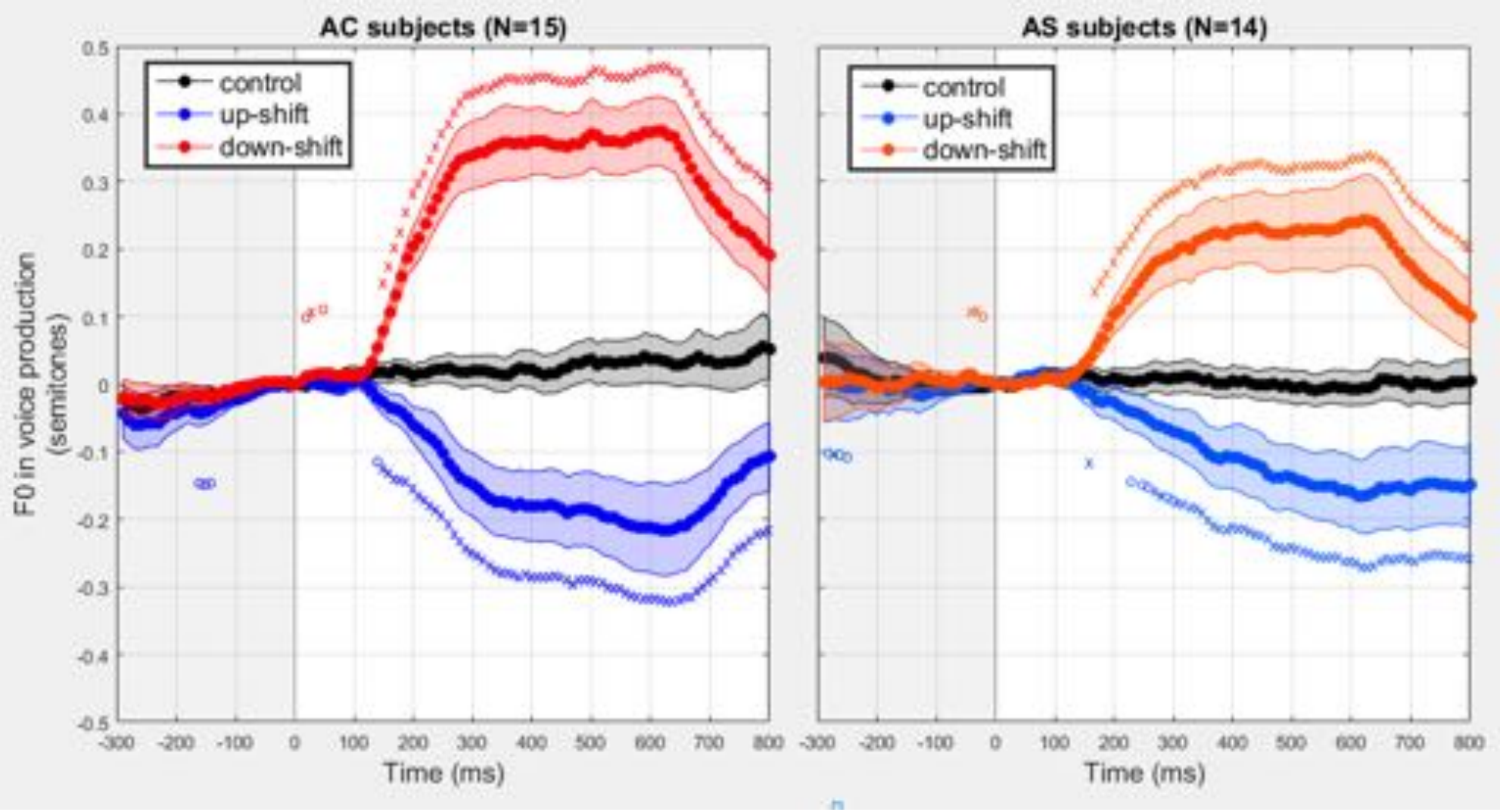




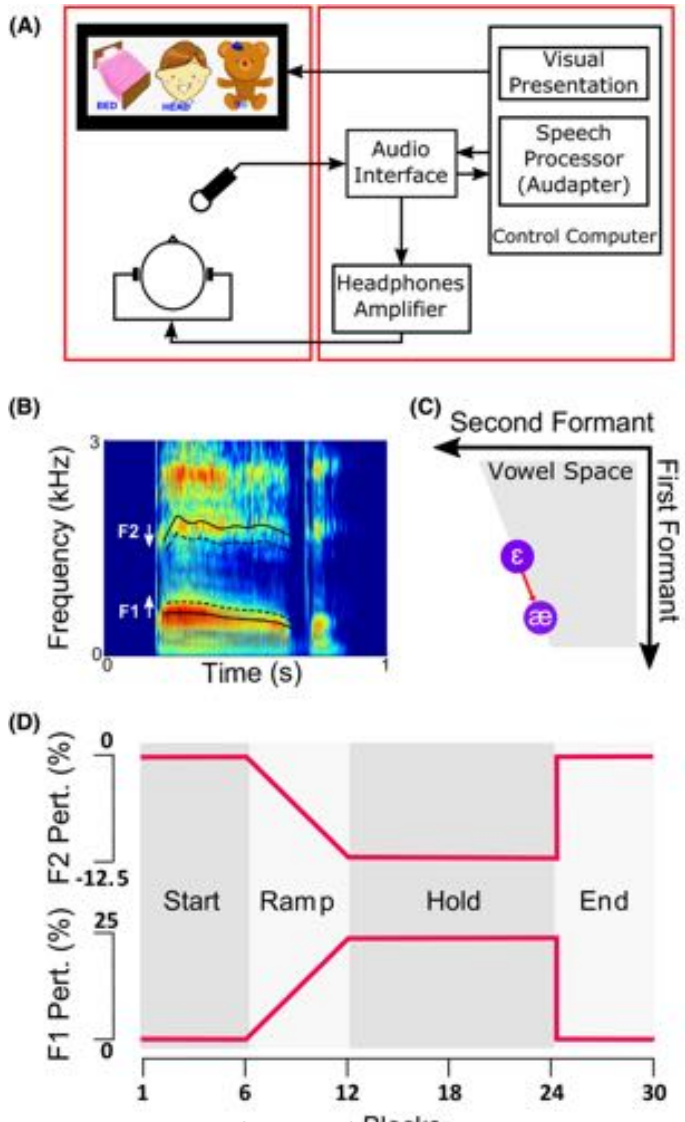
Cai et al. (2012). PloS ONE. Weak Responses to Auditory Feedback Perturbation during Articulation in Persons Who Stutter: Evidence for Abnormal Auditory-Motor Transformation

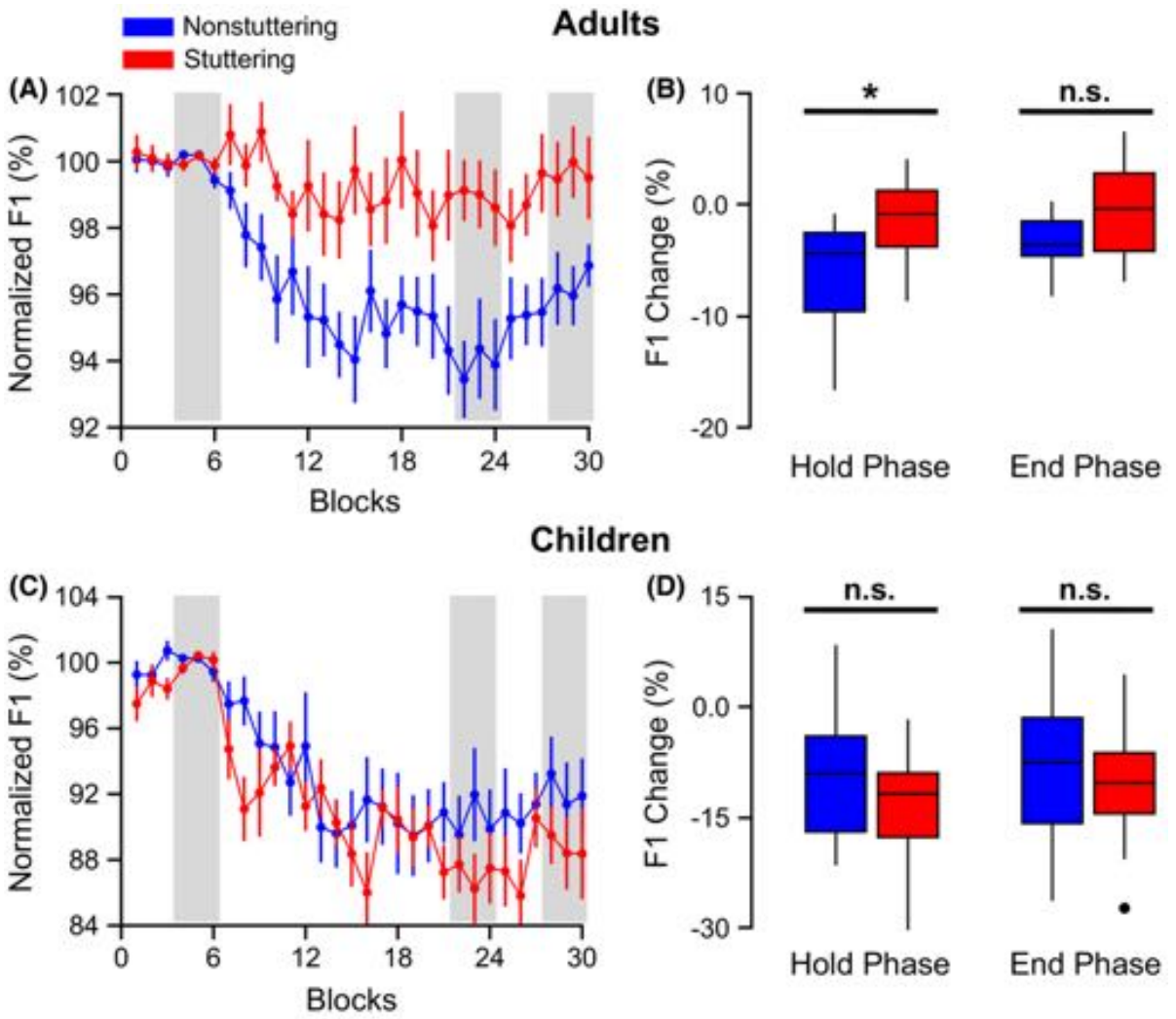

A. F1 compensation in individual subjects (full data set)
PFS
PWS
Down
Up
Fraction F1 change from noPert
Time (ms)
B. Average F1 compensation (full data set)
C. Average F1 compensation (limited data set)
Down (means±1 SEM)
Up (means ± 1 SEM)
Down vs. noPert
Up vs. noPert
Down vs. Up

Auditory feedback--pitch perturbation

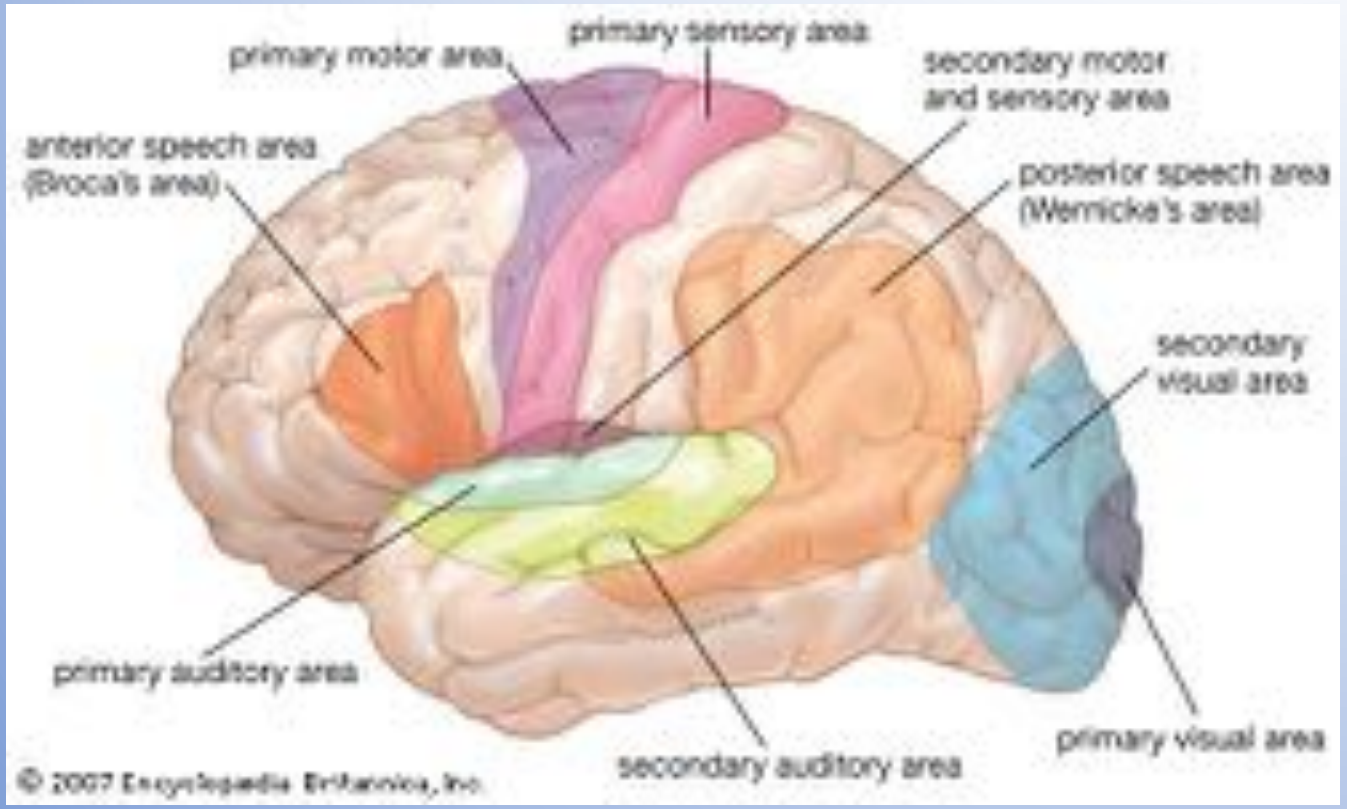


Auditory-motor adaptation is reduced in adults who stutter but not in children who stutter





Developmental Science
2 MAR 2017 DOI: 10.1111/desc.12521
http://onlinelibrary.wiley.com/doi/10.1111/desc.12521/full#desc12521-fig-0001


primary motor area
primary sensory area
secondary motor and sensory area
anterior speech area (Broca's area)
posterior speech area (Wernicke's area)
secondary visual area
primary auditory area
secondary auditory area
primary visual area
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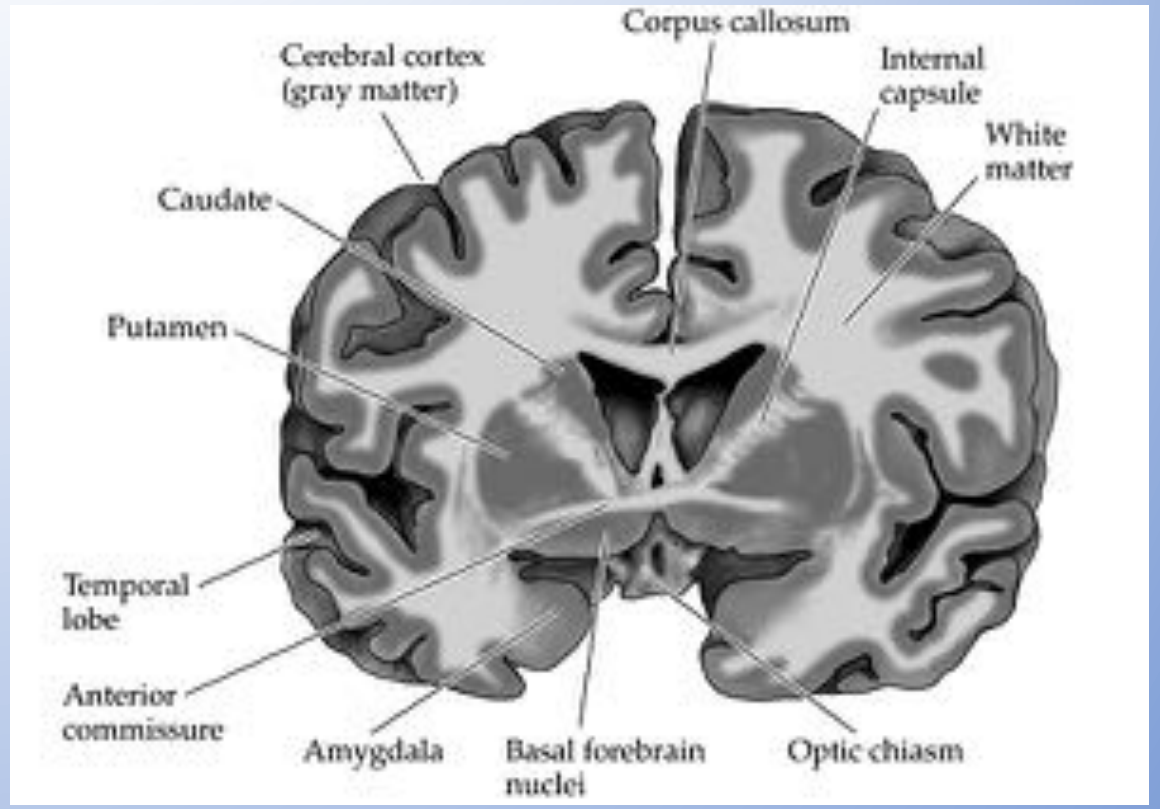
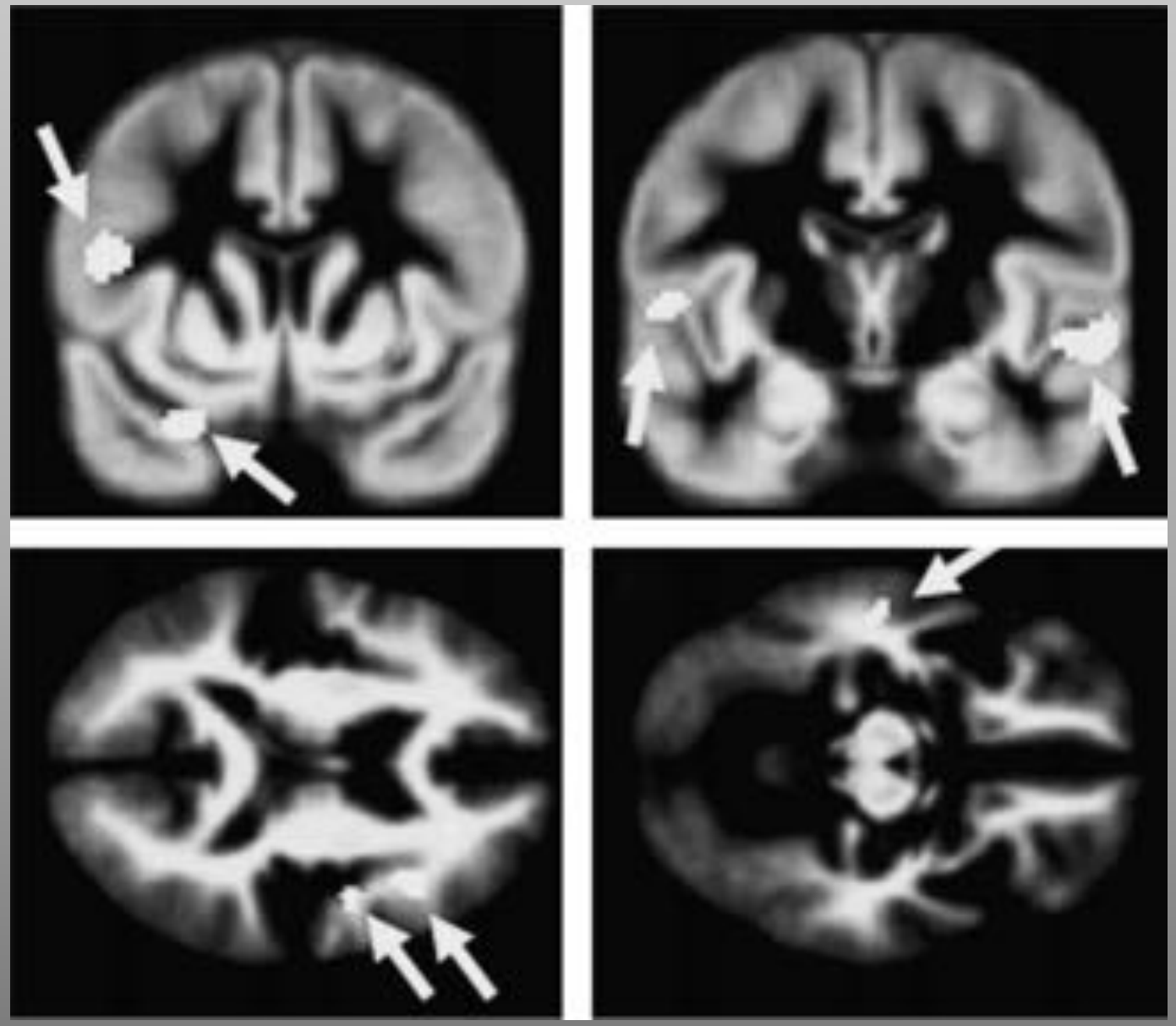

Corpus callosum
Cerebral cortex (gray matter)
Internal capsule
White matter
Caudate
Putamen
Temporal lobe
Anterior commissure
Amygdala
Basal forebrain nuclei
Optic chiasm

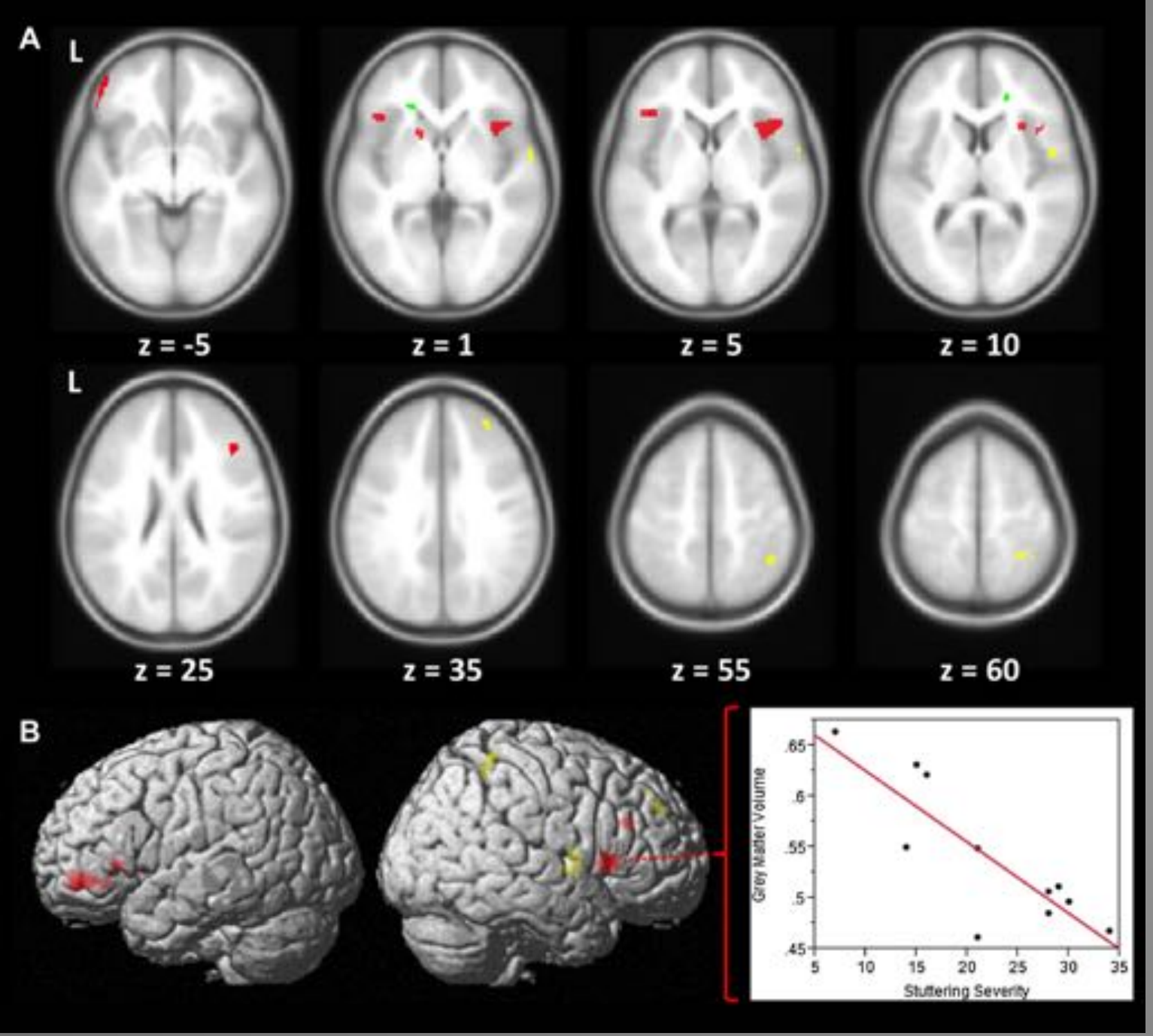
Brain structure

- Voxel based morphometry (VBM)
  - **Voxel-based morphometry** (**VBM**) is a neuroimaging analysis technique that allows investigation of focal differences in brain anatomy, using the statistical approach of statistical parametric mapping.
- Cortical thickness
  - **Cortical thickness** is a **brain** morphometric measure used to describe the combined **thickness** of the layers of the cerebral **cortex**, either in local terms or as a global average for the entire **brain**.
- Diffusion tensor imaging
  - **Diffusion Tensor Imaging** (**DTI**) is an MRI-based neuroimaging technique which makes it possible to estimate the location, orientation, and anisotropy of the brain's white matter tracts.



(a) Coronal view of increased grey matter density in left inferior frontal gyrus and left temporal pole at coordinate y.10. (b) Coronal view of increased grey matter density in left and right superior temporal gyrus at coordinate y.12. (c) Axial view of increased white matter density in two areas of the right insula at coordinate z.14. (d) Axial view of increased white matter density in left middle temporal gyrus at z.14.

Beal et al (2007) NeuroReport. Voxel-based morphometry of auditory and speech-related cortex in stutterers



GMV and WMV
CWS < CWNS (red and green)
CWS > CWNS GMV in yellow
Negative correlation between rIFG GMV and stuttering severity.

Beal et al;., (2013) Cortex A voxel-based morphometry (VBM) analysis of regional grey and white matter volume abnormalities within the speech production network of children who stutter

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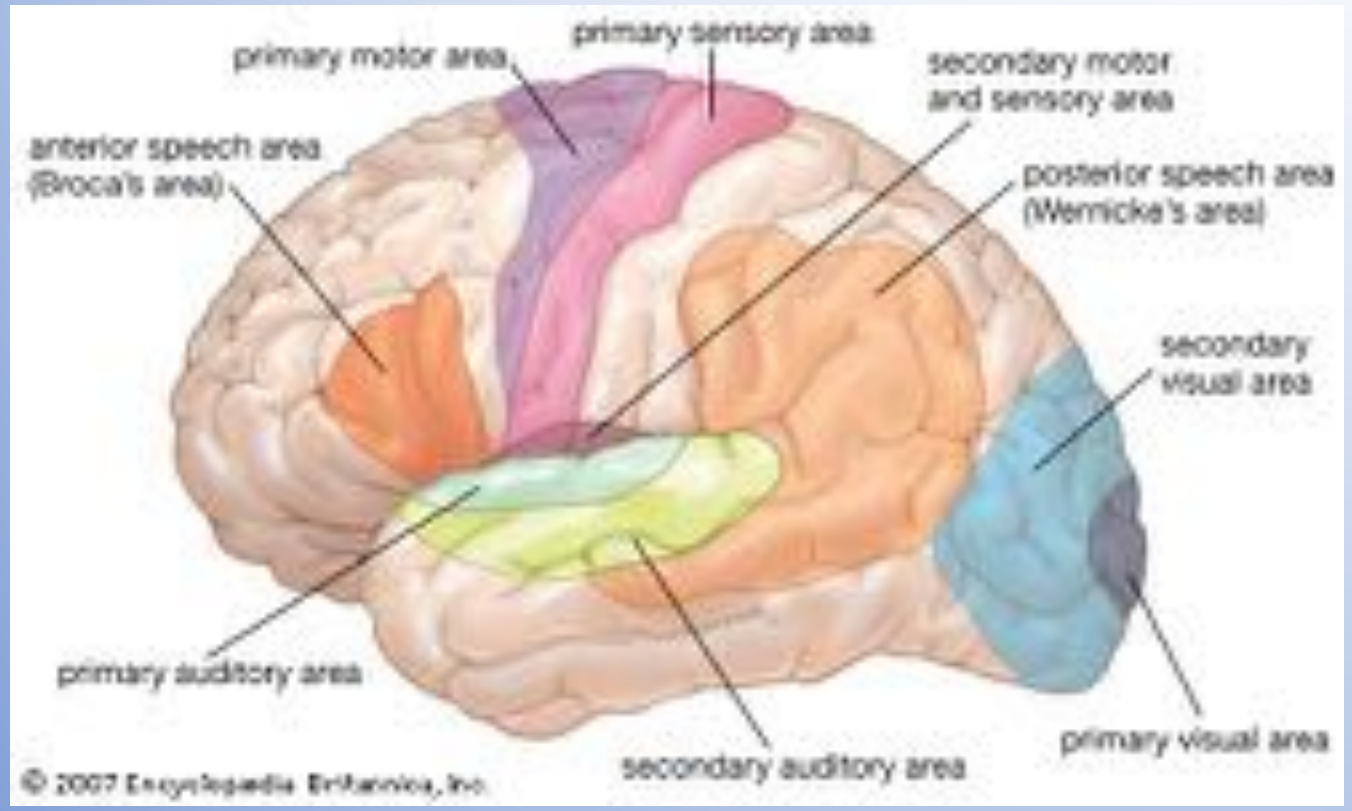
primary motor area
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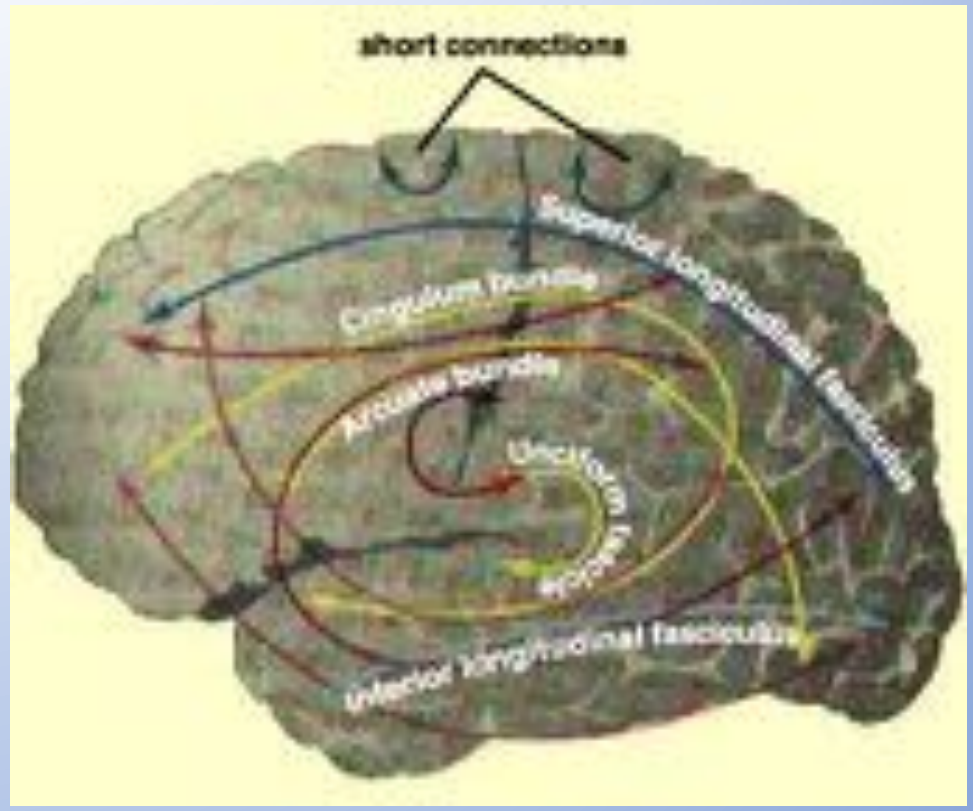
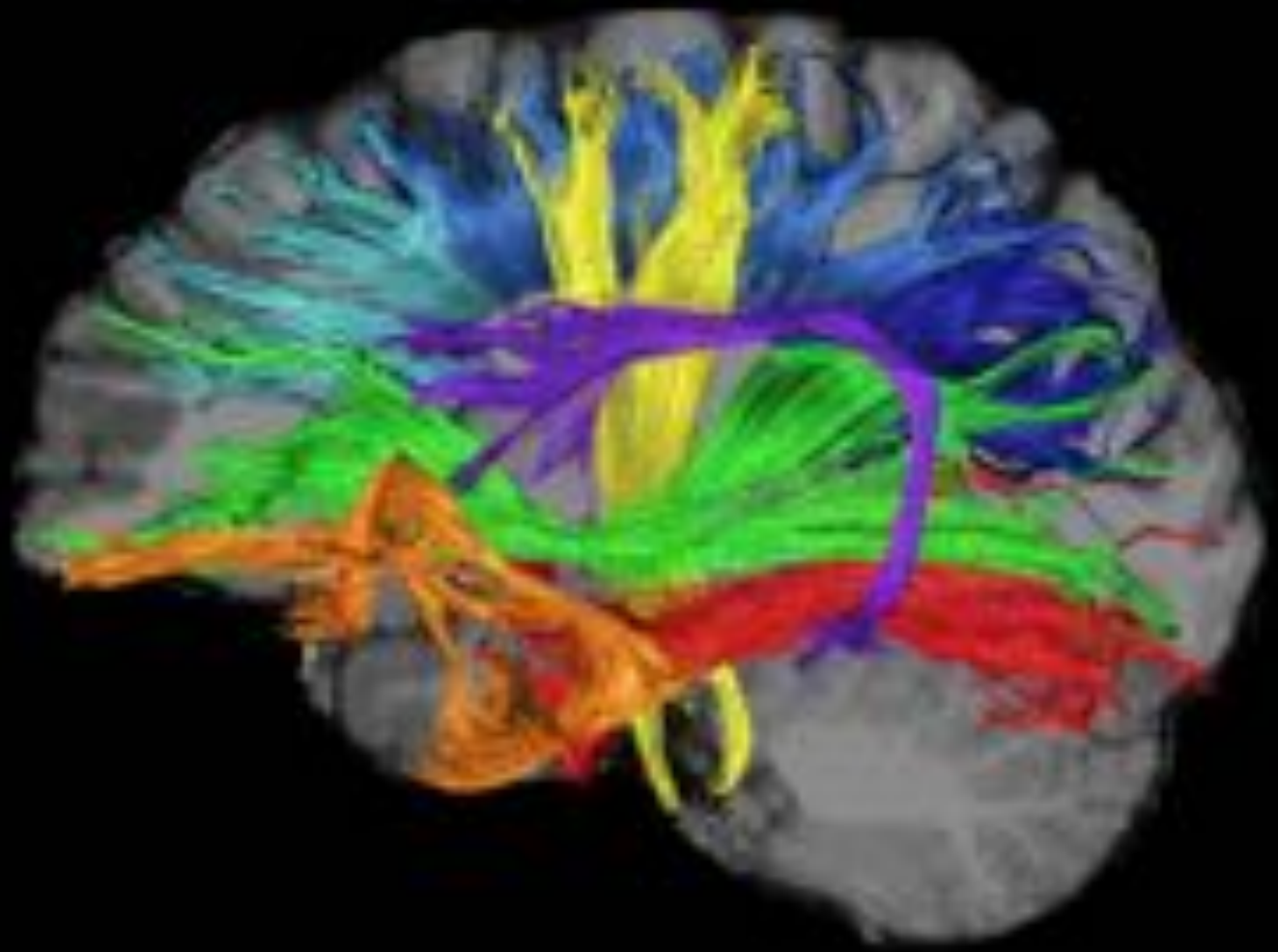
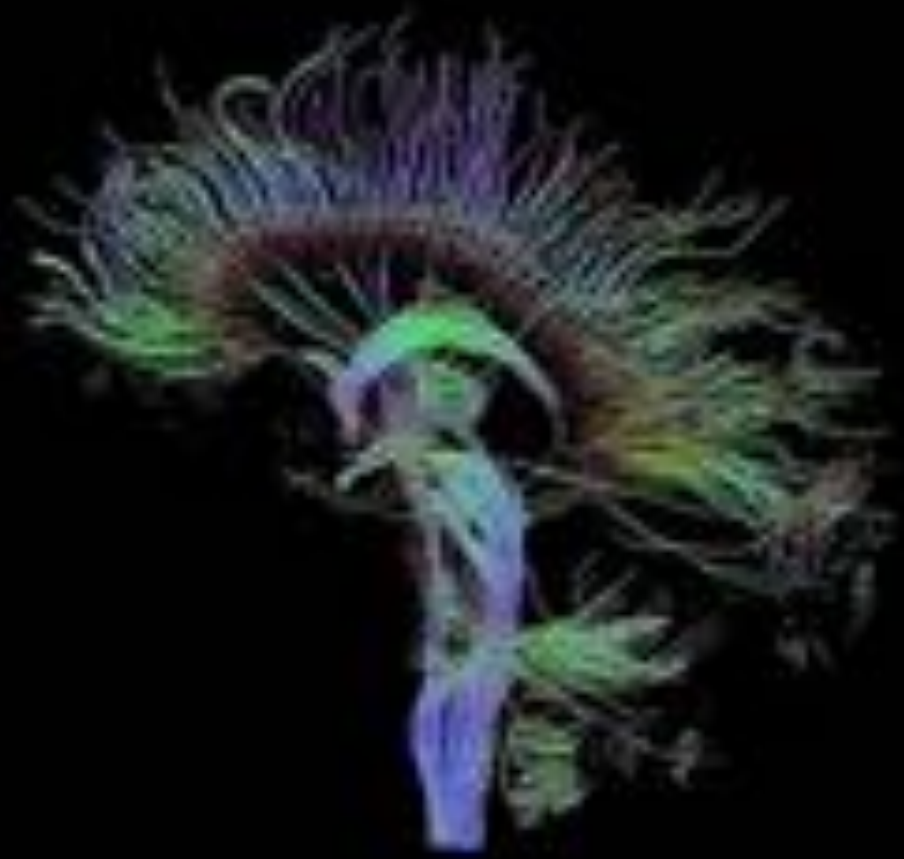

short connections
Cingulum bundle
Arcuate bundle
Uncinate fascicle
inferior longitudinal fasciculus

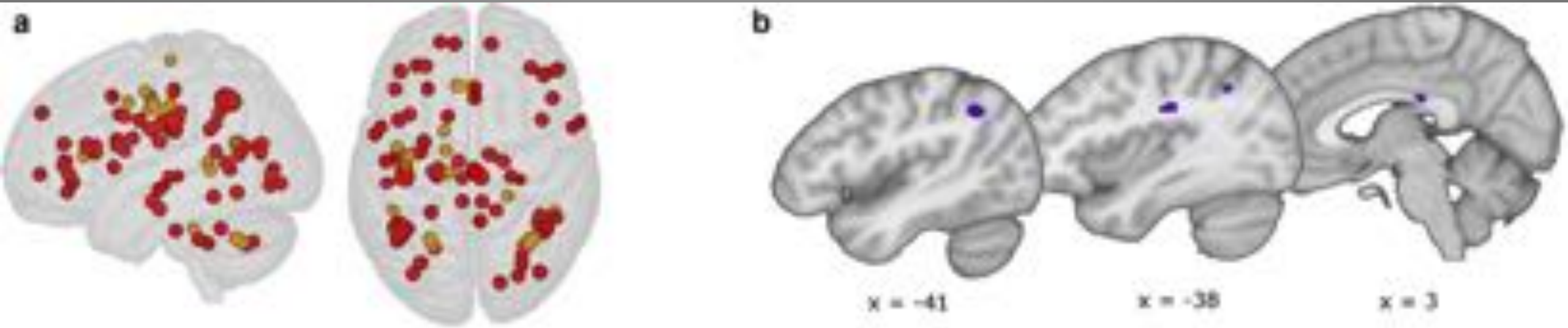
Diffusion tensor imaging





DTI findings (fractional anisotropy measures, FA)

- 9 studies have found reduced FA in PWS
- Few studies have found increased FA (not included here)
- Across studies: 60+ loci of reduced FA in PWS
- Meta-analysis: 3 clusters in left hemisphere (parietal-central) and corpus callosum



Red spheres are from PWS 14-52 years of age; Orange spheres from CWS 3-10 years of age.

Neef et al., (2015). *Curr Neurol Neurosci Rep.* **The neurobiological grounding of persistent stuttering: From structure to function .**

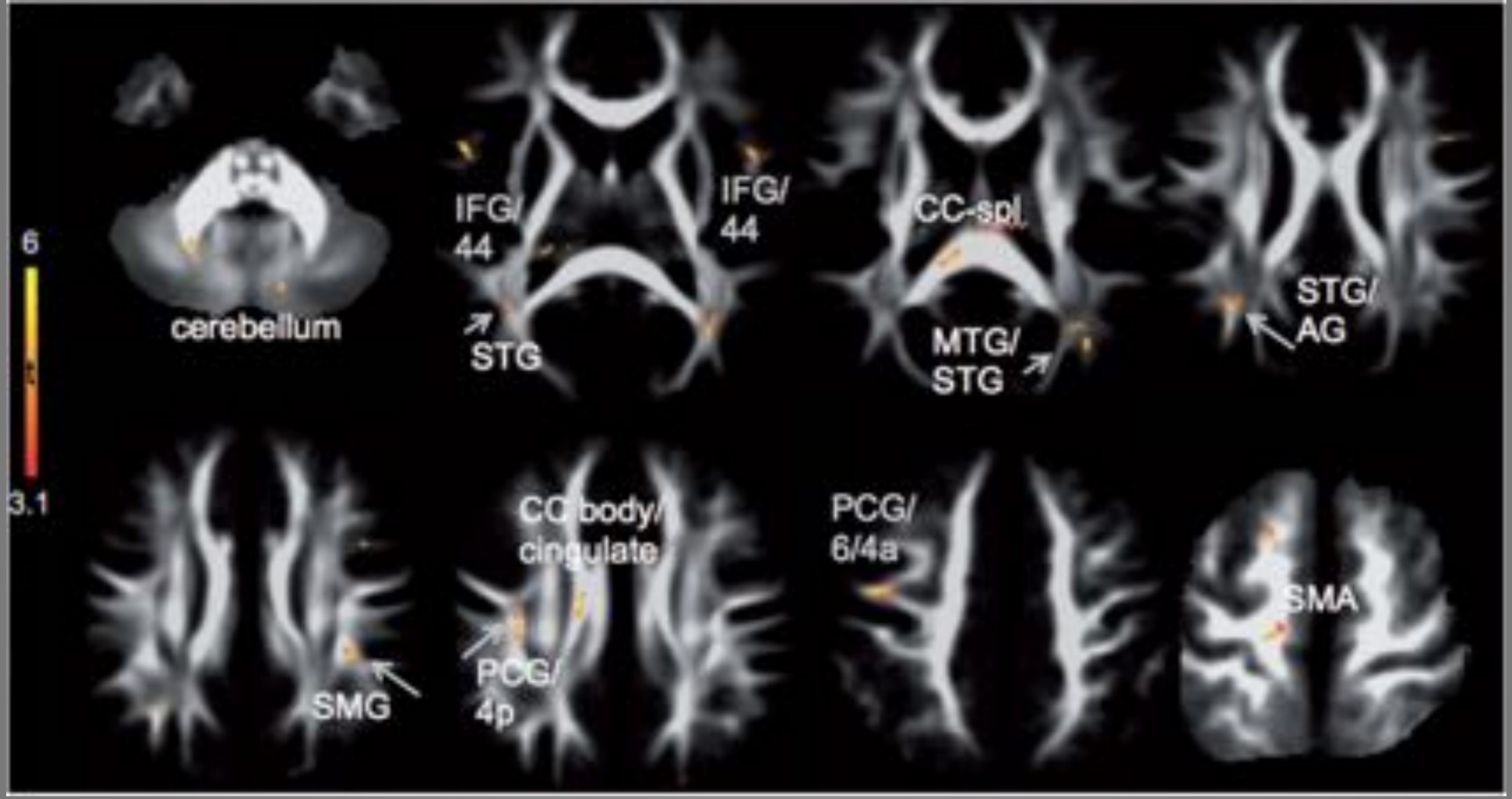


Figure 1 White matter regions showing significant group differences in fractional anisotropy based on whole-brain analysis (TBSS). Coloured highlights show areas with significantly decreased fractional anisotropy in children who stutter compared to controls. AG = angular gyrus; CC-spl = corpus callosum (splenium); PCG = precentral gyrus; SMA = supplementary motor area. S.-E. Chang et al. Brain 2015.

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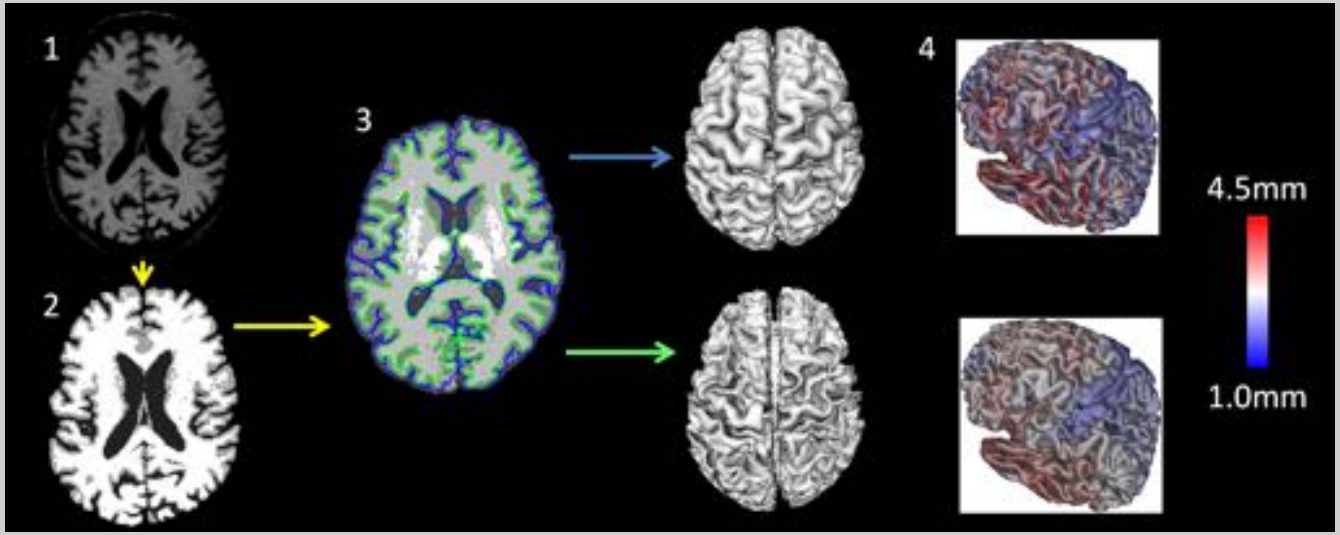
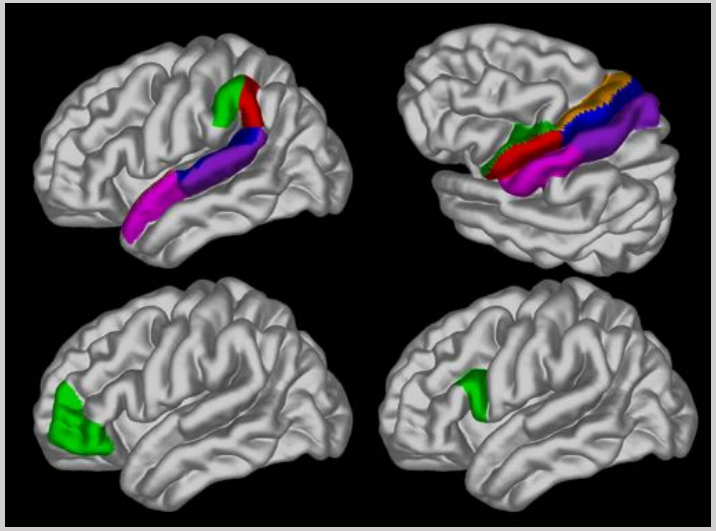
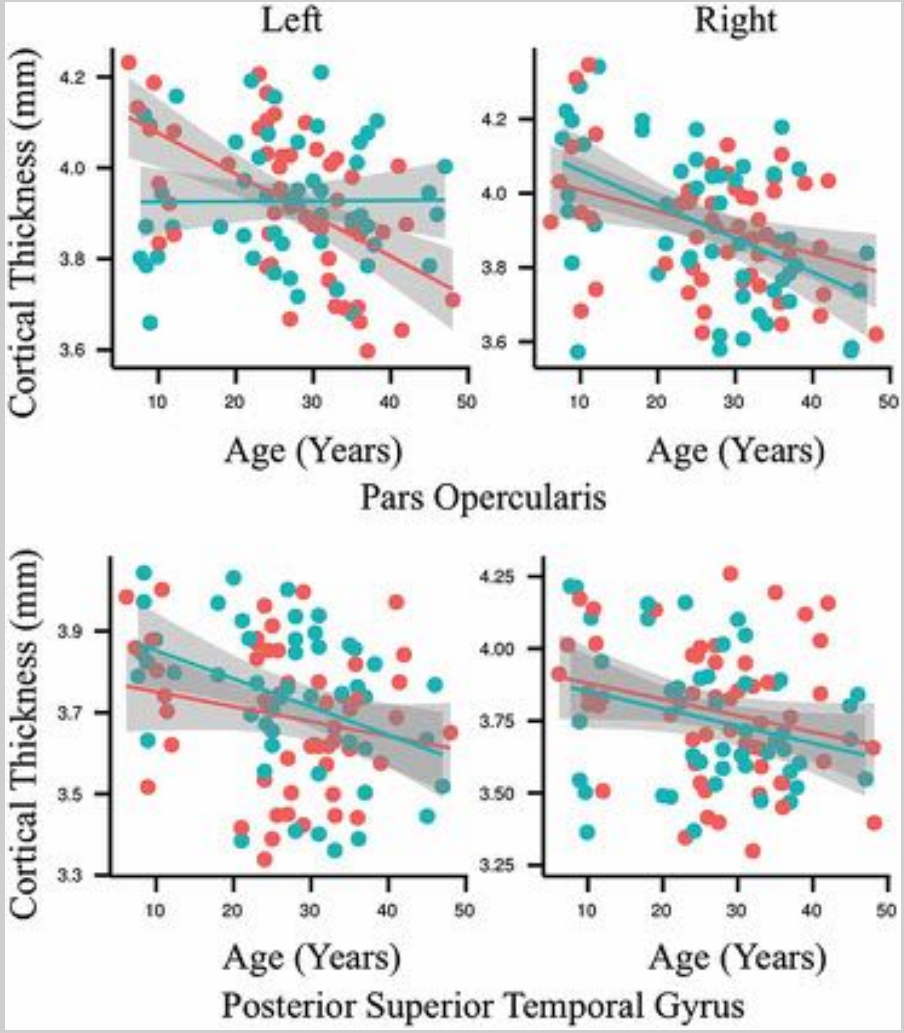
Cortical thickness





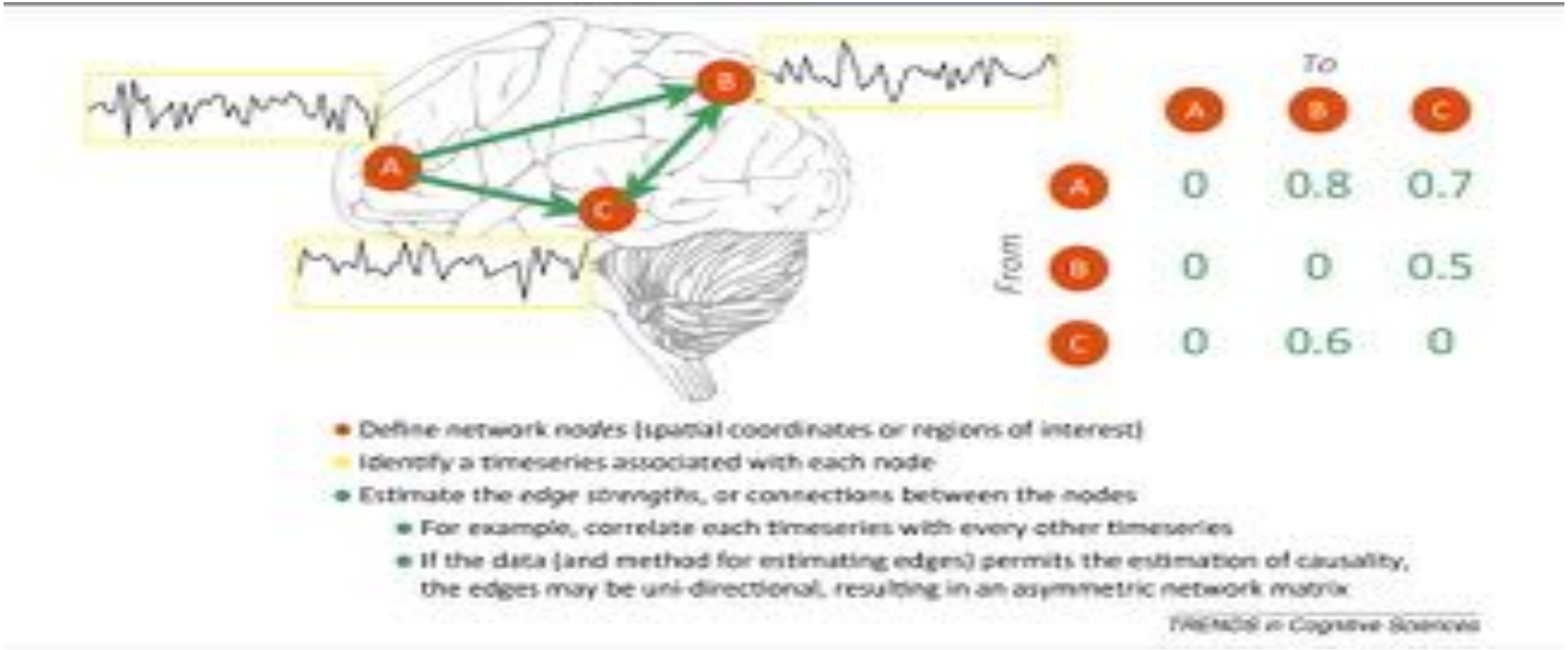


Beal et al., (2015). Frontiers in Human Neuroscience. The trajectory of gray matter development in Broca's area is abnormal in people who stutter

Brain function

- Functional neuroimaging
  - Functional neuroimaging is the use of neuroimaging technology to measure an aspect of brain function, often with a view to understanding the relationship between activity in certain brain areas and specific functional behaviors.
  - Positron emission tomography (PET)
  - MEG/EEG
  - Near infrared spectroscopy (NIRS)
  - Functional magnetic resonance imaging (fMRI)
    - Resting state
    - Task based

Resting state connectivity



as a means to identify functional networks

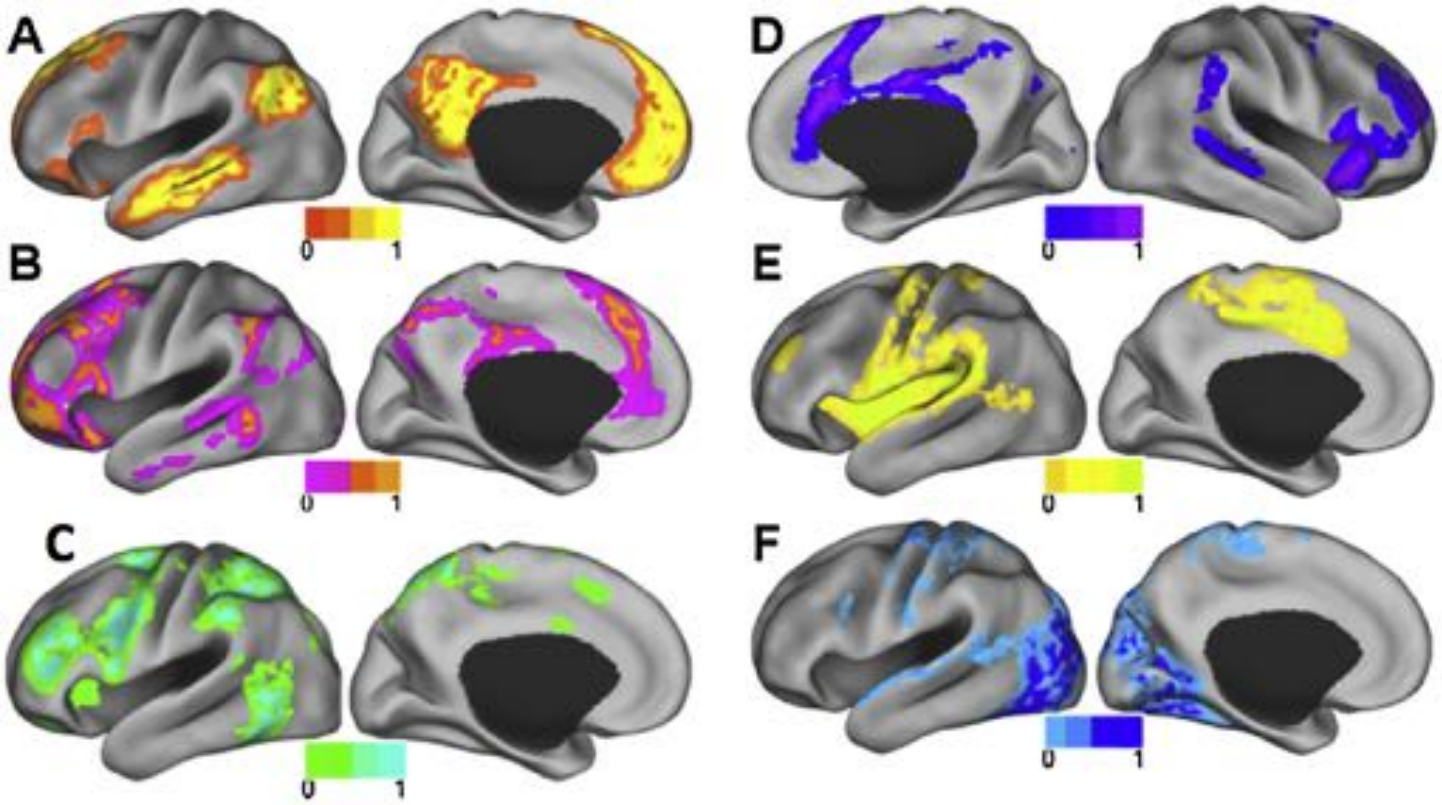


Fig. 1. A–F. Resting state intrinsic connectivity networks (ICNs) examined in this study. A) Default mode network (DMN), B) Frontoparietal network (FPN),C) Dorsal attention network (DAN), D) Ventral attention network (VAN), E) Somatomotor network (SMN), F) Visual network (VN).

Chang, S. -E., et al. Anomalous network architecture of the resting brain in children who stutter. Journal of Fluency Disorders (2017), http://dx.doi.org/10.1016/j.jfludis.2017.01.002

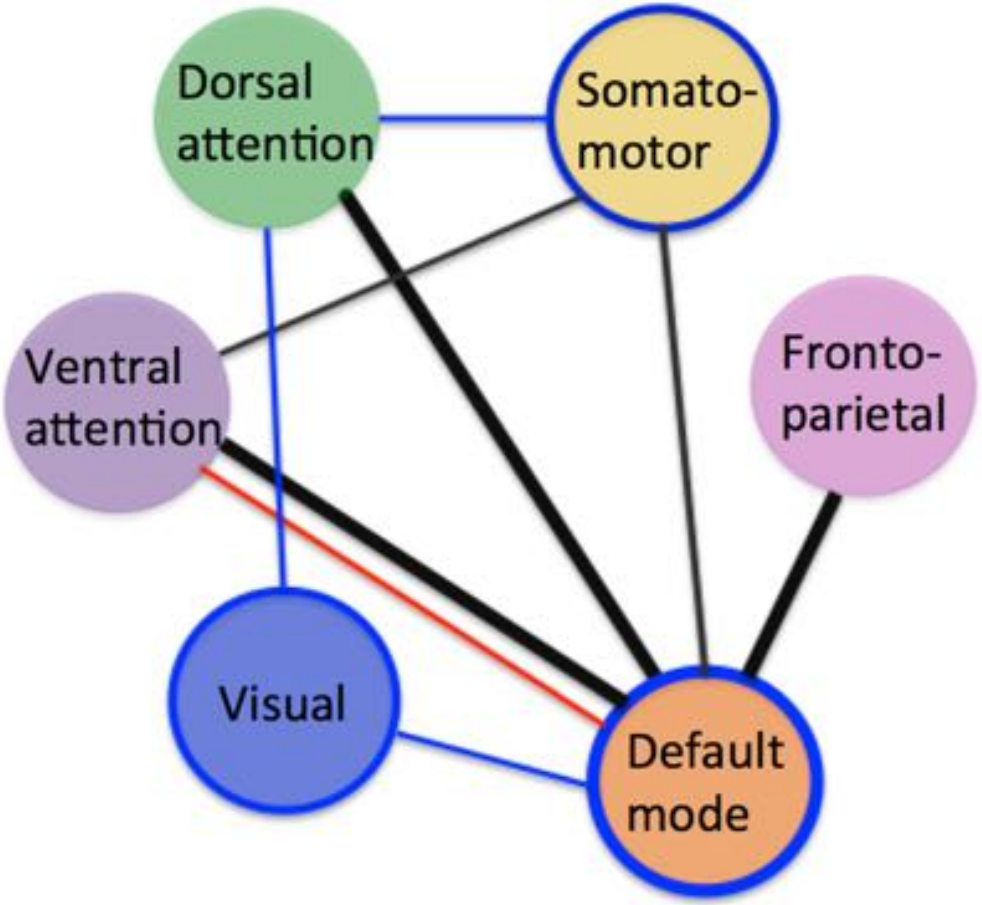
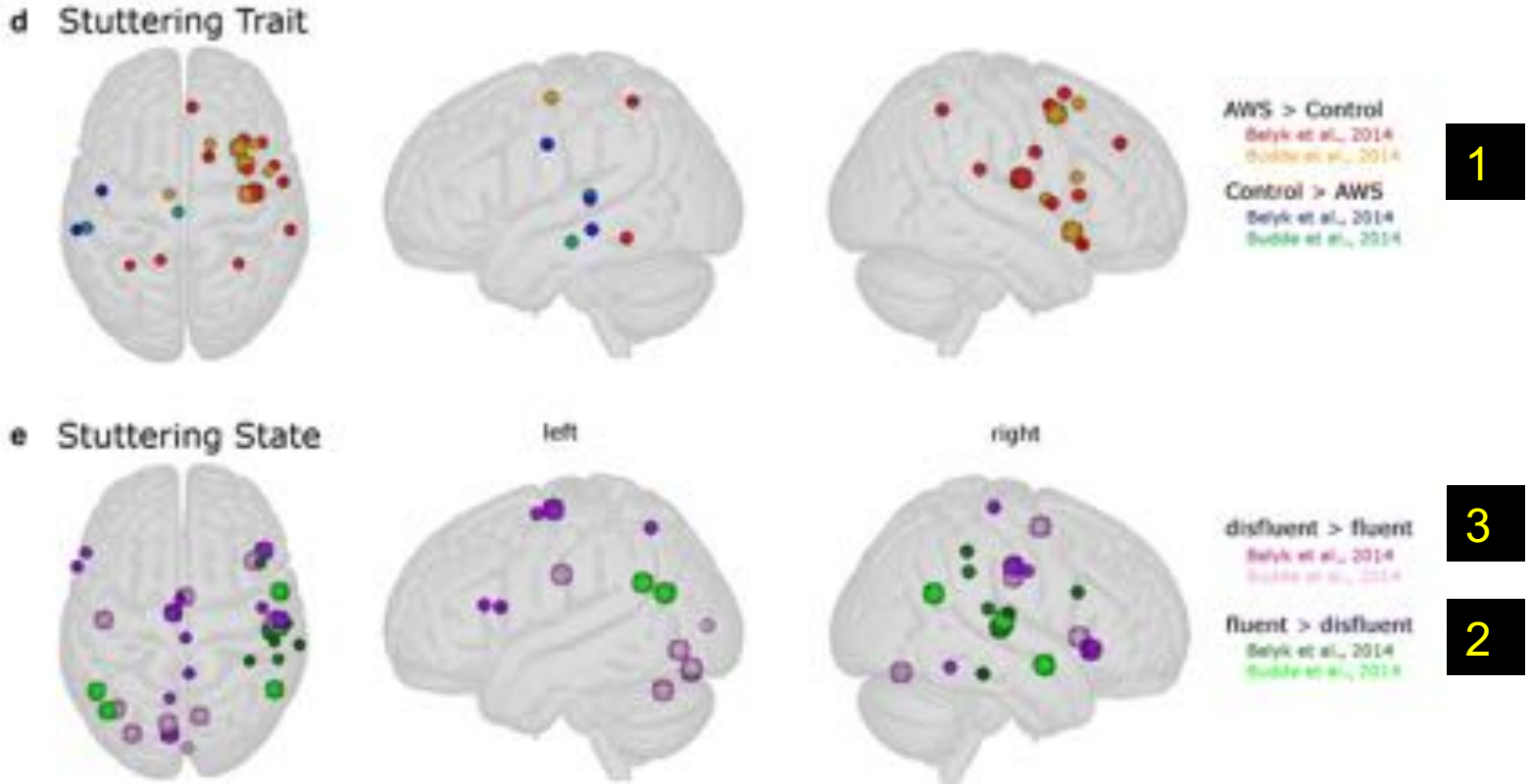


Fig. 6. Lines indicate connections expressed to a greater extent in CWS; thick lines are connections associated with stuttering persistence. Blue lines indicate decreased connectivity; red lines, increased connectivity. Black lines are anomalous connectivity in CWS. Blue border is significant intra-network connectivity decreases in CWS.

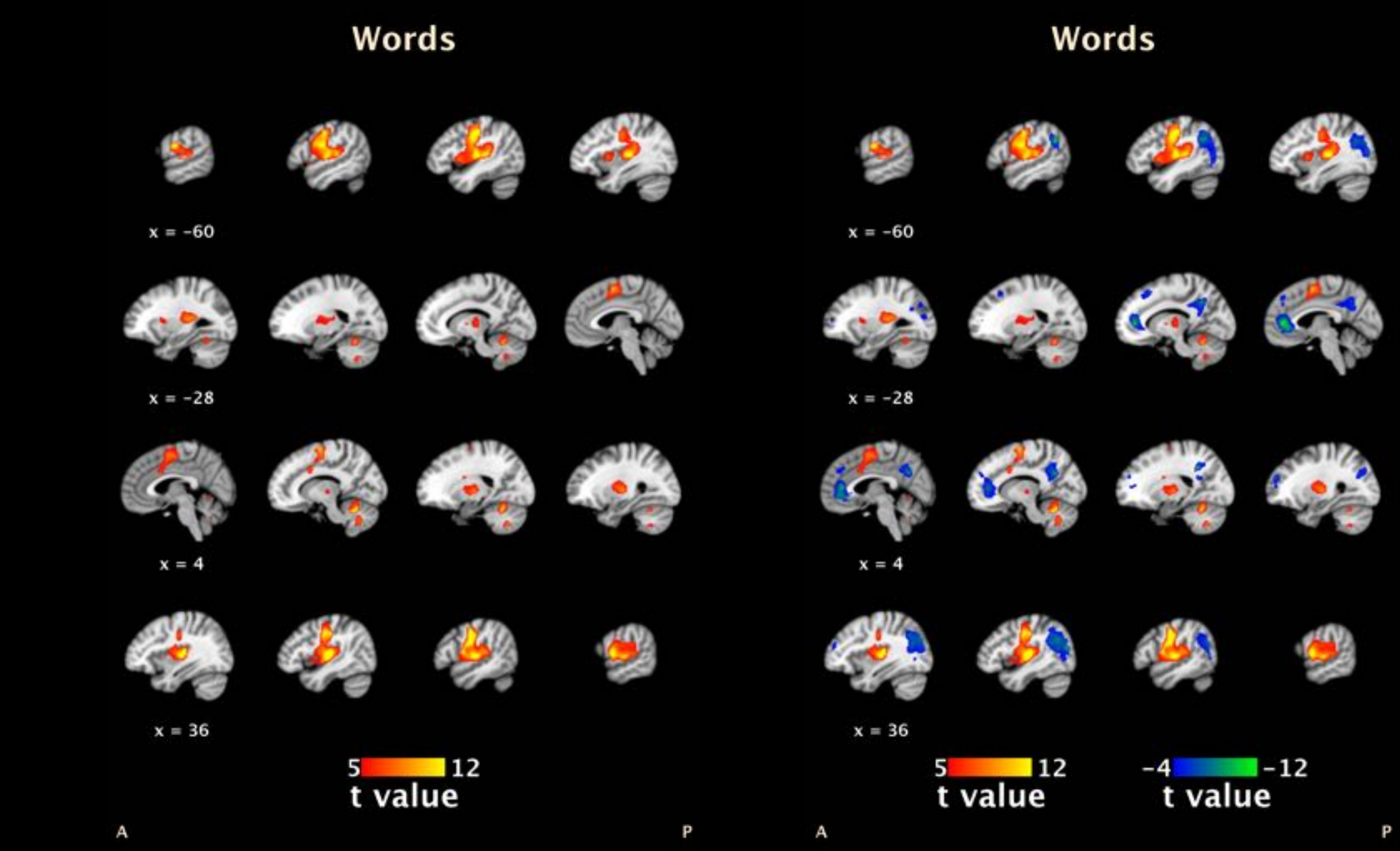
Functional imaging findings

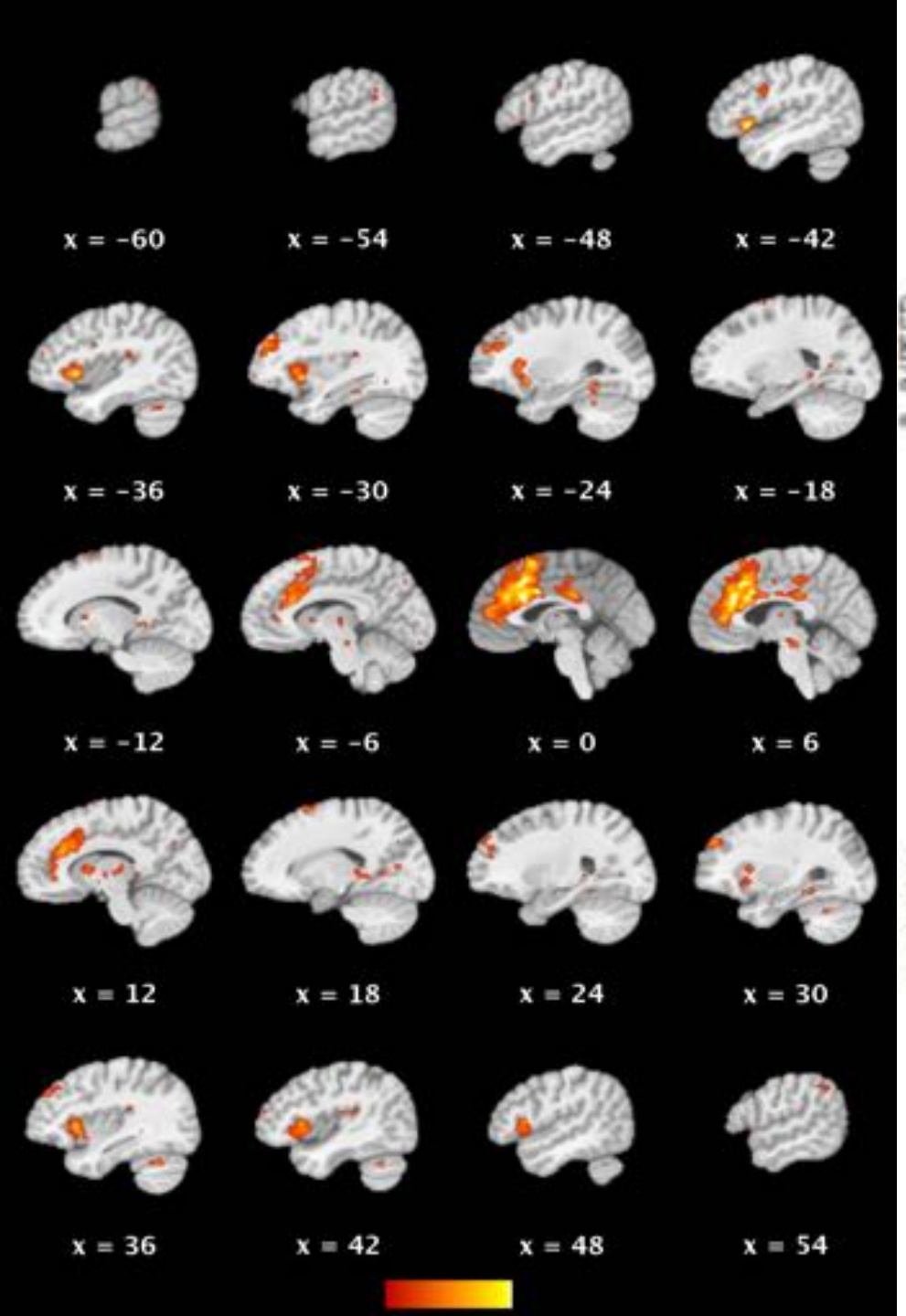
- PWS show right-hemisphere over-activation of sensorimotor areas (including M1, PMC, pre-SMA, SMA, IFG, RO) and left-hemisphere under-activation of temporal regions.
- Increased fluency in PWS is associated with increased activation of superior temporal regions in both hemispheres.
- Increased stuttering in PWS is associated with increased activation of inferior frontal regions in both hemispheres.

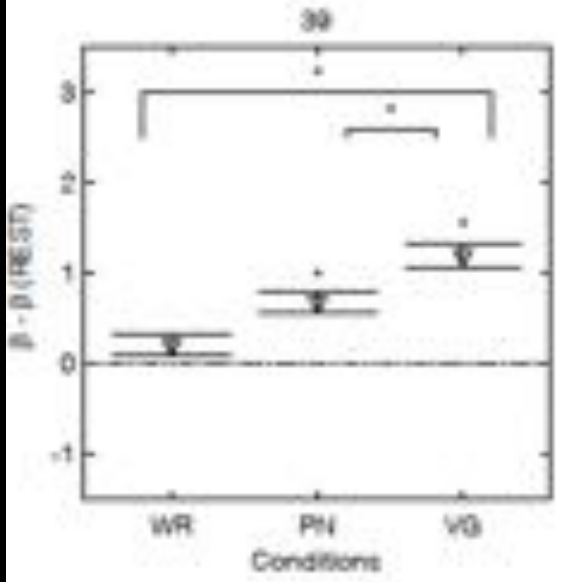


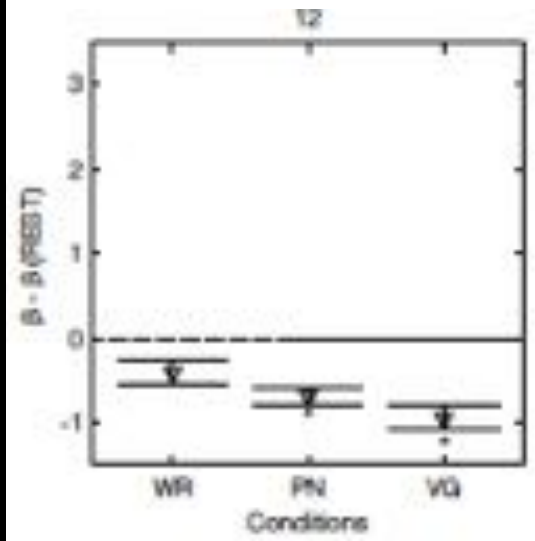
Blood Oxygen-Level-Dependent (BOLD) signal

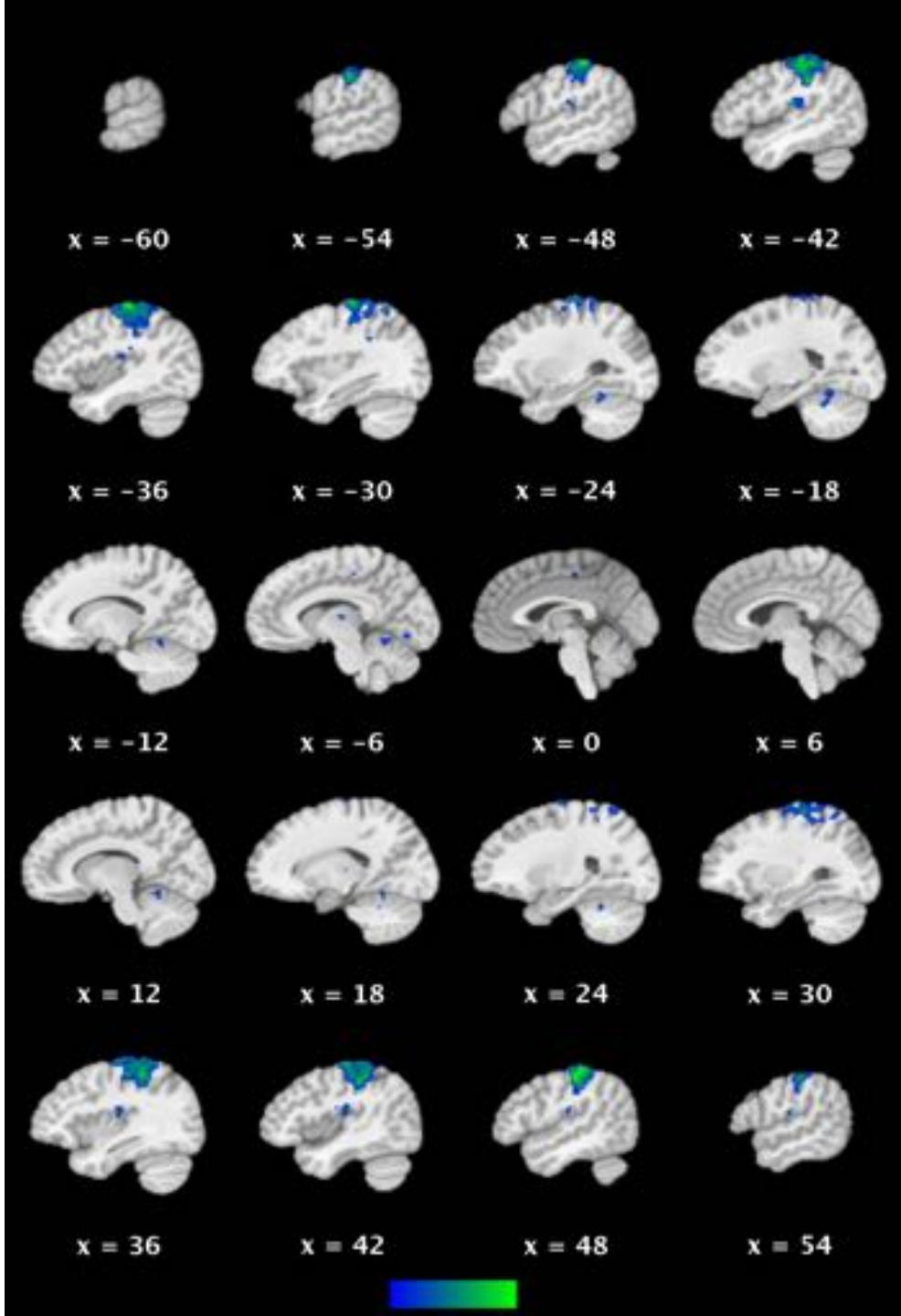
- Much of what we know, think we know, want to know about speech production (or any other human behavior) comes from studies employing fMRI.
- The fMRI signal reflects the synaptic activity driving neuronal assemblies.
- Positive BOLD response (PBR) corresponding to excitatory activation (LFP, MUA, excitatory neurotransmitters).
- Negative BOLD response (NBR) is a marker of neuronal deactivation (inhibition) reflecting metabolic and hemodynamic downregulation.
- NBR observed relative to rest or to task contrast.


Words
x = -60
x = -28
x = 4
x = 36
5
12
t value
A
P
Words
x = -60
x = -28
x = 4
x = 36
5
12
t value
-4
-12
t value
A
P


x = -60
x = -54
x = -48
x = -42
x = -36
x = -30
x = -24
x = -18
x = -12
x = -6
x = 0
x = 6
x = 12
x = 18
x = 24
x = 30
x = 36
x = 42
x = 48
x = 54


39
WR
PN
VG
Conditions


12
WR
PN
VG
Conditions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x = -54
x = -48
x = -42
x = -36
x = -30
x = -24
x = -18
x = -12
x = -6
x = 0
x = 6
x = 12
x = 18
x = 24
x = 30
x = 36
x = 42
x = 48
x = 54

Some final thoughts about stuttering and research directions

- Speech is regulated by co–activated functional brain networks and their dysfunction results in persistent stuttering.
- The dysfunction results from a combination of structural and functional differences that are in need of reduction into a coherent theoretical framework.
- There is a need to identify the primary factors underlying stuttering in children and how experience modulates the neural environment as the disorder persists (research on children and adults).
- To identify the antecedent events in the brain to predict the onset of stuttering episodes.
- Use this information in conjunction with clinical protocols to identify casual factors, facilitate treatment and develop new treatment approaches.