

Reduced activation of left orbitofrontal cortex precedes blocked vocalization: A magnetoencephalographic study

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ARTICLE INFO

Article history:

Received 1 March 2012
Received in revised form 28 April 2012
Accepted 6 May 2012
Available online 19 May 2012

Keywords:

Stuttering
Brain-imaging
Blocking
Magnetoencephalography (MEG)
Sensorimotor integration

ABSTRACT

While stuttering is known to be characterized by anomalous brain activations during speech, very little data is available describing brain activations during stuttering. To our knowledge there are no reports describing brain activations that precede blocking. In this case report we present magnetoencephalographic data from a person who stutters who had significant instances of blocking whilst performing a vowel production task. This unique data set has allowed us to compare the brain activations leading up to a block with those leading up to successful production. Surprisingly, the results are very consistent with data comparing fluent production in stutterers to controls. We show here that 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. This data adds weight to the argument forwarded by [Kell et al. \(2009\)](#) that the best functional sign of optimal repair in stuttering is activation of the left BA 47/12 in the orbitofrontal cortex.

Educational objectives: At the end of this activity the reader will be able to (a) identify brain regions associated with blocked vocalization, (b) discuss the functions of the orbitofrontal and inferior frontal cortices in regard to speech production and (c) describe the usefulness and limitations of magnetoencephalography (MEG) in stuttering research.

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1. Introduction

Stuttering is a speech disorder of neurological origin. Brain imaging studies have shown that, compared to control subjects, people who stutter (PWS) exhibit significantly different patterns of neural activity during fluent speech production (for review see [Brown, Ingham, Ingham, Laird, & Fox, 2005](#)). However, little is known about how activity in the brains of PWS may differ during stuttering compared to their brain activity during fluent speech. This is largely because it is difficult to systematically observe stuttering in brain imaging settings, for several reasons.

In the laboratory it is often the case that PWS stutter less than they normally would. Further, the experimental tasks that are compatible with current brain research methods – e.g. single word or syllable production – typically do not induce enough instances of stuttered speech to include stuttered speech as a condition (e.g. see [Salmelin, Schnitzler, Schmitz, & Freund, 2000](#)). Because of this many studies simply discard stuttered epochs from their analysis (e.g. [Chang, Kenney, Loucks, & Ludlow, 2009](#); [Salmelin et al., 2000](#)). An alternative strategy is to continuously sample speech during a scanning block and to retroactively correlate brain activations with the degree of stuttered speech (e.g. [Braun et al., 1997](#); [Fox et al.,](#)

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2000). Consequently, measurements of brain activations that are directly associated with stuttering instances are rare in the literature (with a few notable exceptions, e.g. Ingham, Fox, Costello Ingham, & Zamarrripa, 2000).

We report here a rare case in which we were able to record ~100 instances of both blocked and non-blocked vocalization from a PWS subject. The subject was a participant in a larger magnetoencephalography (MEG) study utilizing a stop signal paradigm to assess the extent of voluntary inhibitory control of vocalization in PWS. The subject was unable to complete the main study due to the high frequency of blocking. However this unusual case provided a unique opportunity to assess brain activity preceding unambiguous instances of vocalization blocking.

2. Method

2.1. Participant

The participant was a 24-year-old right-handed female. Her stuttering began at the age of 7. She has an older sister and uncle with stuttering histories. Her diagnosis of stuttering was confirmed by a speech pathologist and her severity was rated as 4 (on a scale from 1 to 10 where 1 = no stuttering 10 = most severe stuttering imaginable). The subject reported that this severity was typical of her stuttering but that it fluctuates between 3 and 8. At assessment she produced 1428 syllables at a rate of 198 syllables per minute. 3.9% of these syllables were stuttered. Stuttering during assessment consisted of blocks, repetitions of words and fillers. She had no other significant medical history.

This study was approved by the Macquarie University Human Ethics Committee # R06420.

2.2. Stimuli and apparatus

The task used in this experiment was the same Stop Signal task as that described in detail in Etchell, Sowman, and Johnson (2012). As the subject was unable to perform the task due to high frequency of blocking we describe only the 'Go' trial part of the experiment which was used in this report. Go trials began with a black fixation cross appearing in the centre of a grey background. The duration of the fixation cross was randomly varied between 1000 ms and 3500 ms after which time, a black letter (either I or O) against a white background surrounded by a green border appeared in the centre of the screen. The letter I appeared on half the trials and the letter O appeared on the other half and their order was randomized. The subject was instructed to respond to the letters by making the sound of the letter O as it would occur in the word "hot" or making the sound of the letter I as it would occur in the word "hit". Vocalizations were recorded by a directional microphone positioned on the ceiling of the magnetically shielded room above the subject's head.

The experimental presentation was controlled by the Presentation software package (Presentation 14.4, Neurobehavioral Systems, Albany, USA). The stimuli were projected via a mirror onto a screen, which was directly in the participant's line of sight. The subject was equipped with a button which she was instructed to activate after any trial on which stuttering or blocking occurred.

2.3. Data acquisition

Brain activity was recorded with a whole-head MEG system (Model PQ1 160R-N2, KIT, Kanazawa, Japan) consisting of 160 coaxial first-order gradiometers with a 50 mm baseline (Kado et al., 1999; Uehara et al., 2003). Prior to MEG measurements, five marker coils were placed on the participant's head and their positions and the participant's head shape were measured with a pen digitizer (Polhemus Fastrack, Colchester, VT). Head position was measured by energizing the marker coils in the MEG dewar immediately before and after the recording session. MEG was sampled at 1 kHz and band-pass filtered between 0.03 and 200 Hz.

A T1-weighted, structural MRI scan was obtained in a separate session using a 3T Siemens Verio scanner at Macquarie University Hospital, Marsfield, NSW, Australia. Scans were 1 mm isotropic.

MEG signals were bandpass filtered between 1 and 45 Hz. Epochs of 200 ms duration (1000 ms preceding and 1000 ms following the onset of the Go signal) were sorted into those where a response was executed ("successful vocalization") and those where there was no response recorded and the subject indicated that blocking had occurred ("unsuccessful vocalization"). The epochs thus categorized were analyzed using SPM8 (Ashburner et al., 2009). Artefacts including blinks and eye-movements were removed using the artefact rejection tool implemented in SPM8. A total of 98 successful vocalizations and 134 unsuccessful vocalizations were recorded. Data were averaged and a 2D topographical representation of the evoked field for each sample of the time dimension across the epoch of interest was created for each of the 2000 samples between -1000 and 1000 ms around the stimulus onset. For display purposes these images were cropped to show between -200 and 800 ms around the stimulus onset (Fig. 1). The averaged event-related fields (ERFs) were visually examined and then passed forward to the inversion analysis.

2.4. Source space analysis

The MEG coordinate system was transformed into the Montreal Neurological Institute (MNI) coordinate system. A canonical cortical mesh derived from the MNI template was warped, in a nonlinear manner, to match the participant's structural

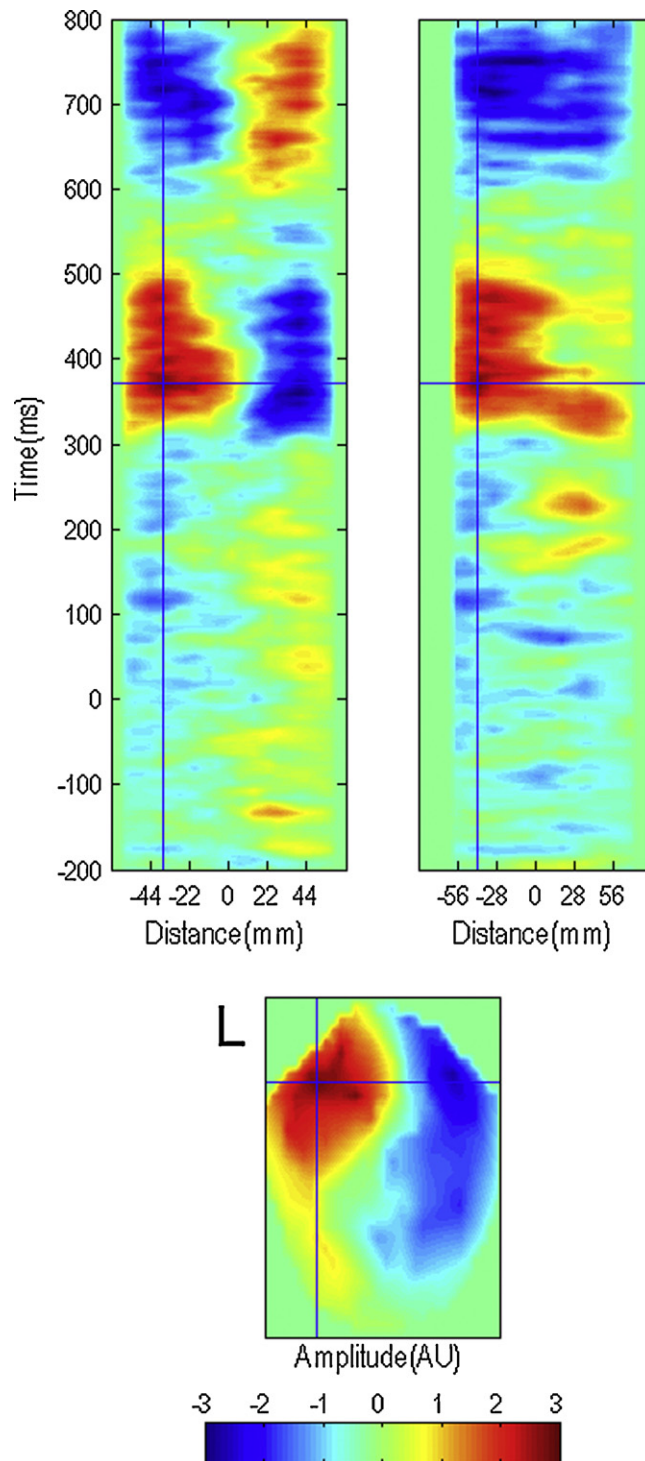


Fig. 1. Sensor space results for the difference between successful vocalization and unsuccessful vocalization. Cross hairs indicate the location in time and space of the peak difference between successful and unsuccessful vocalization. The bottom image is a 2D x–y space interpolated from the flattened electrode locations at one point in time (the max difference between successful and unsuccessful vocalization). The two top images are sections through x and y respectively, expressed over time (vertical (z) dimension). Distance indicated in the x dimension (lefthand plots) is lateral from the centre. Distance indicated in the x dimension (righthand plots) is anterior and posterior from the centre. The anterior of the head is oriented toward the top of the page. The y-axis indicates peristimulus time with time zero being the onset of the go signal.

MRI scan. Based on a single sphere model, the ensuing mesh was entered into a forward model computation of the source lead fields.

Source localization was carried out on the averaged ERFs using the Greedy Search method implemented in SPM8. It results in a spatial projection of sensor data into (3D) brain space and considers brain activity as comprising a very large number of dipolar sources spread over the cortical sheet, with fixed locations and orientations (Litvak et al., 2011). The evoked activity for each dipolar source was estimated within two time windows where it was evident that there was a divergence in the averaged ERFs between successful and unsuccessful vocalization. These 2 time windows were 300–600 ms post-stimulus onset and 600–800 ms post-stimulus onset.

A further 2 time windows (–300 to –600 ms and –600 to –800 ms) from the prestimulus epoch were also inverted in order to provide baseline activation levels. The maximum and minimum differences between the baselines for each condition were used as thresholds for the detection of significant differences between the post-stimulus activations when successful and unsuccessful vocalization were compared. Only difference clusters larger than 50 voxels were considered significant. Functional brain activations were projected onto a glass brain for visualization.

3. Results

3.1. Reaction time

On average the subject had a vocal reaction time for the successful vocalization trials of 863 ± 37 ms.

3.2. Sensor space analysis

Following the onset of the Go signal the averaged ERFs showed that, compared to unsuccessful vocalization, the ERF for successful vocalization was characterized by a larger deflections centred on 400 ms and 700 ms. Over the left hemisphere the ~400 ms deflection was positive in polarity and the ~700 ms deflection negative. The reverse was true for the right hemisphere. These differences were most pronounced over anterior sensors (Fig. 1).

3.3. Source space analysis

3.3.1. Epoch 1: 300–600 ms post-stimulus onset

3.3.1.1. Sources where activation for successful vocalization was greater than unsuccessful vocalization. The largest difference in the source space analysis between successful vocalization and unsuccessful vocalization in the 300–600 ms window was a large, extra activation for an area that encompassed the left inferior frontal and orbitofrontal lobes, including Brodmann area 47. The difference was more than 50 times larger than the largest positive difference in the equivalent prestimulus period comparison. A second difference cluster, where successful vocalization was greater than unsuccessful vocalization, occurred in the left middle frontal gyrus including Brodmann area 10. This difference was more than 10 times larger than the largest positive difference in the equivalent prestimulus period (Fig. 2).

3.3.1.2. Sources where activation for unsuccessful vocalization was greater than successful vocalization. A large negative difference between successful vocalization and unsuccessful vocalization occurred bilaterally over the inferior part of the pre and post central gyri including Brodmann areas 3 and 4. The peak difference was greatest on the left hemisphere, being approximately 20 times the magnitude of the largest negative difference in the equivalent prestimulus period. The second

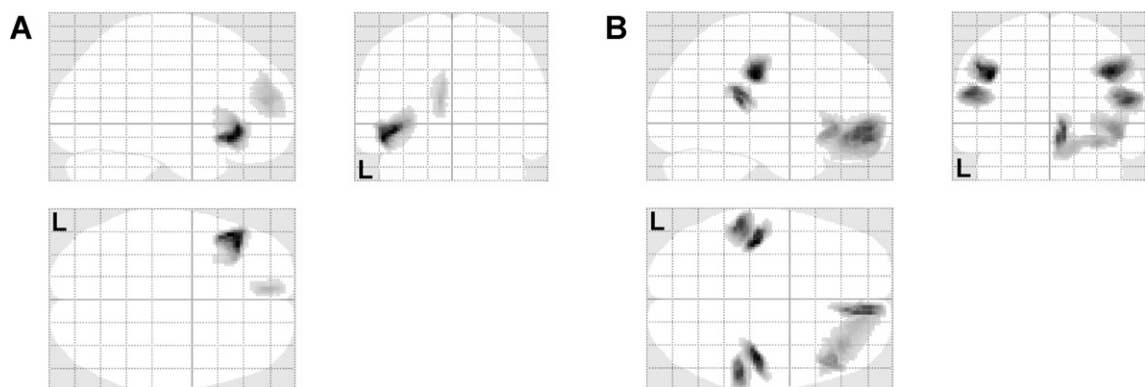


Fig. 2. Source space results for the epoch 300–600 ms post-stimulus. (A) Sources where the response for successful vocalization was greater than unsuccessful vocalization. (B) Sources where the response for unsuccessful vocalization was greater than successful vocalization. The left side is marked by an "L".

largest difference occurred bilaterally over an area that incorporated parts of the superior temporal gyrus and the inferior part of the posterior parietal lobe. The clusters incorporated parts of Brodmann areas 13, 40, 41 and 42 and were more than 15 times larger than the equivalent prestimulus difference. There was greater activation for unsuccessful vocalization compared to successful vocalization in a cluster that extended from the right medial frontal lobe including Brodmann area 10 through to the right inferior frontal and orbitofrontal lobes including Brodmann area 47. The peak differences in these clusters were more than 9 times greater than the peak negative difference between the baseline epochs.

3.3.2. Epoch 2: 600–800 ms after stimulus onset

3.3.2.1. *Sources where activation for successful vocalization was greater than unsuccessful vocalization.* The largest difference in the source space analysis between the go response and the unsuccessful responses in the 600–800 ms window was an extra activation preceding successful vocalization for an area that encompassed the left inferior frontal lobe, left temporal pole and fusiform gyrus including Brodmann area 20.

4. Discussion

The current study demonstrates, for the first time, a significant difference in brain activation preceding blocking as compared to successful production in an adult PWS. Significantly, this data shows that early activation of left hemispheric orbitofrontal regions is associated with successful vocalization. This finding is significant in that it directly relates to the finding that increased left hemispheric activation in an area that incorporates BA47 is the best correlate of functional recovery from stuttering (Kell et al., 2009). Furthermore, a number of studies have shown that, in PWS, both the grey matter and the white matter constituting the left inferior frontal/orbito-frontal cortex are abnormal (Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Chang et al., 2009; Sommer, Koch, Paulus, Weiller, & Buchel, 2002; Watkins, Smith, Davis, & Howell, 2008) and that BA47 is relatively deactivated during overt speech in stutterers (Fox et al., 1996; Ingham et al., 2000).

Given that the data discussed in the current study comes from a single subject and that lateralization of language for this subject has not been established, caution must be taken when interpreting the significance of lateralized activation. Nonetheless it is useful to consider the differences in activation in terms of both their laterality and strength in regards to previous studies of brain activity in stuttering. The current study demonstrates that, even in an unrecovered stutterer, increased early activation of the left BA47 is associated with successful instances of initiation of vocalization. This area is involved in integration of sensory and motor information (Kringelbach, O'Doherty, Rolls, & Andrews, 2003) and is proposed to be integral to the integration of sensory information into the speech motor program (Kell et al., 2009).

We also found there was extra activation on the unsuccessful vocalization trials at a latency of 300–600 ms in sensorimotor areas associated with articulation (Kell et al., 2009). In agreement with a number of other authors who have shown relative overactivation of motor areas in stuttering, we suggest that these reflect the extra effort required to overcome the vocalization block.

With regard to the overactivation of those areas associated with auditory processing (Brodmann areas 13, 40, 41 and 42), we posit that these anomalies could be a downstream consequence of the relative underactivation of inferior frontal regions which are involved in the propagation of efference copies of vocalization commands back to the auditory cortex (Liu, Behroozmand, Larson, & Stefan, 2010). Failure of efference copy processes, which act in part to dampen reafference, have previously been implicated in the etiology of stuttering (Brown et al., 2005; Maraist & Hutton, 1957). Furthermore, auditory overactivations (Chang et al., 2009; Kell et al., 2009) and disordered suppression of self-stimulation during vocalization (Beal et al., 2010) are both evident in stuttering.

In the later stages of pre-vocalization there was a trend toward a reversal of this pattern. For failed compared to successful vocalizations there was an increased activation of the left inferior frontal gyrus and orbitofrontal cortices between 600 and 800 ms after stimulus onset. The difference was much smaller than the earlier extra activation in the same area for successful vocalization, possibly representing a delayed, weaker activation of a critical locus for vocalization. A further small increase in the activation of the left inferior temporal lobe was also noted in the same period for successful activations compared to unsuccessful activation. Caution must be observed when interpreting the differences in this late epoch however, as a number of trials that were included in the source analysis may include the beginnings of vocalization, and therefore be different precisely because there is a degree of motoric activation and/or sensory reafference present.

5. Limitations

The scope of the current data is limited in regards to its generalizability. We have examined a single subject who presented with severe blocking symptoms. While her severity on assessment was only mild to moderate, the exacerbation of her symptoms under the unique environment imposed by the experimental protocol suggest an underlying susceptibility to the peculiar demands of the task that, in its full scope, required periodic response inhibition from the subject. While the current subject had no history of treatment for, or diagnosis of Tourette syndrome [associated with atypical response inhibition (Stern, Blair, & Peterson, 2008)] and did have a clear history of developmental stuttering, our clinical assessment methods may have been insensitive to an atypical presentation. We used percent syllables stuttered and an arbitrary severity score to characterize the subject's stuttering; both measures have been shown to be reliable (O'Brian, Packman, Onslow, & O'Brian,

2004), however, their specificity might not have been great enough to access the unique features of this subject's stuttering. On the other hand the ability to reliably identify sub-types in stuttering remains elusive (Yairi, 2007).

6. Summary

These data show abnormal activation of the inferior frontal and orbitofrontal lobes in a PWS subject. Reduced activation of the left BA47 in particular was associated with failed initiation of speech. These findings are consistent with reports of disordered activation and connectivity of the left BA47 in stuttering. Furthermore, overactivation of auditory areas and the articulation area (inferior primary motor and somatosensory cortices) were evident in the trials where speech initiation failed.

CONTINUING EDUCATION

QUESTIONS

- Which of the following methodologies was used to record brain activations?
 - Functional magnetic resonance imaging (fMRI)
 - Electroencephalography (EEG)
 - Positron emission tomography (PET)
 - Magnetoencephalography (MEG)
 - Transcranial magnetic stimulation (TMS)
- Preceding blocked vocalizations brain activation was reduced compared to successful vocalization in the:
 - Left inferior frontal and orbitofrontal lobes
 - Right inferior frontal and orbitofrontal lobes
 - Cerebellum
 - Left posterior parietal lobe
- Preceding blocked vocalizations brain activation was increased compared to successful vocalization in the:
 - Cerebellum
 - Left posterior parietal lobe
 - Inferior part of the pre and post central gyri
 - Left inferior frontal and orbitofrontal lobes
- According to Kell et al. (2009) the best brain correlate of functional recovery from stuttering is
 - Activation in Brodmann area 2
 - Activation in Brodmann area 6
 - Activation in Brodmann area 47
 - Activation in Brodmann area 40
- The left Brodmann area 47 is thought to be involved in
 - Integration of sensory and motor information
 - Inhibition of action
 - Regulation of rhythm and timing
 - Planning speech
 - Thermoregulation

Acknowledgements

PFS is a training fellow of the NHMRC, Australia (#543438). This research was supported by an NHMRC of Australia research grant (#1003760) and was also supported by the Australian Research Council Centre of Excellence for Cognition and its Disorders (CE110001021) <http://www.ccd.edu.au>. The authors would like to acknowledge comments and suggestions on the manuscript provided by Dr. Anna Hearne.

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Stephen Crain, Ph.D., came to Macquarie University in 2004 and set up the KIT-Macquarie Brain Research Laboratory, which houses two MEG systems. He is the Director of the ARC Centre of Excellence in Cognition and its Disorders, which investigates five areas of cognition (language, reading, belief formation, memory, and person perception). The Centre is a collaboration between researchers at Macquarie University, University of Western Australia and University of New South Wales, and at international locations. The last decade of his research has focused on children's acquisition of semantic knowledge, in particular young children's knowledge of logical operators. Much of this research has been cross-linguistic, with a particular focus on Mandarin Chinese.

Elisabeth Harrison, Ph.D., before joining the Department of Linguistics at Macquarie University in 2003, she worked as a Senior Speech Pathologist in the Stuttering Unit, Bankstown Health Service. She has been on the Board of Directors of the Australian Stuttering Foundation since 1999 and is an Honorary Research Associate of the Australian Stuttering Research Centre, the University of Sydney. She teaches a variety of subjects at Macquarie University at the undergraduate and postgraduate level. Her current research interests are the Lidcombe Program of early stuttering intervention, early language development and the onset of stuttering, and the application of evidence based practice in speech pathology. Her Ph.D. dissertation reported the first attempts to dismantle the Lidcombe Program and to investigate how its treatment components work.

Blake W. Johnson, Ph.D., investigates the mechanisms of visual and auditory perception, mental imagery, and action representation in the human brain. He combines techniques from cognitive and perceptual psychology for measuring human performance, with neuroscientific techniques for measurement of human brain function and structure. He is particularly interested in techniques that have very high temporal resolution for brain activity, including electroencephalography (EEG) and magnetoencephalography (MEG).