# Global Motor Inhibition Precedes Stuttering Events

Joan Orpella[1*], Graham Flick[1], M. Florencia Assaneo[2], Liina Pylkkänen[134], David Poeppel[156], Eric S. Jackson[7*]

[1]Department of Psychology, New York University, USA

[2]Institute of Neurobiology, National Autonomous University of Mexico, Juriquilla, Querétaro, Mexico

[3]Department of Linguistics, New York University, USA

[4]NYUAD Institute, New York University Abu Dhabi, United Arab Emirates

[5]Center for Language, Music and Emotion (CLaME), New York University, New York, NY, USA

[6]Ernst Strüngmann Institute (ESI) for Neuroscience, Frankfurt, Germany

[7]Department of Communicative Sciences and Disorders, New York University, USA

*Corresponding authors

Joan Orpella

jo1358@nyu.edu

Eric S. Jackson

eric.s.jackson@nyu.edu

# Abstract

Research points to neurofunctional differences underlying fluent speech production in stutterers and non-stutterers. There has been considerably less work focusing on the processes that underlie *stuttered* speech, primarily due to the difficulty of reliably eliciting stuttering in the unnatural contexts associated with neuroimaging experiments. We used magnetoencephalography (MEG) to test the hypothesis that stuttering events result from global motor inhibition–a "freeze" response typically characterized by increased beta power in nodes of the action-stopping network. We leveraged a novel clinical interview to develop participant-specific stimuli in order to elicit a comparable amount of stuttered and fluent trials. Twenty-nine adult stutterers participated. The paradigm included a cue prior to a go signal, which allowed us to isolate processes associated with stuttered and fluent trials prior to speech initiation. During this pre-speech time window, stuttered trials were associated with greater beta power in the right pre-supplementary motor area, a key node in the action-stopping network, compared to fluent trials. Beta power in the right pre-supplementary area was related to a clinical measure of stuttering severity. We also found that anticipated words identified independently by participants were stuttered more often than those generated by the researchers, which were based on the participants' reported anticipated sounds. This suggests that global motor inhibition results from stuttering anticipation. This study represents the largest comparison of stuttered and fluent speech to date. The findings provide a foundation for clinical trials that test the efficacy of neuromodulation on stuttering. Moreover, our study demonstrates the feasibility of using our approach for eliciting stuttering during MEG and functional magnetic resonance imaging experiments so that the neurobiological bases of stuttered speech can be further elucidated.

**Keywords:** Stuttering; Fluency; Global Motor Inhibition; pre-SMA; MEG

**Abbreviations:** CBGTC = cortico-basal ganglia-thalamocortical; dSPM = dynamic statistical parameter mapping; MEG = magnetoencephalography; R-DLPFC = right dorsolateral prefrontal cortex; SSI-4 = stuttering severity index - 4th edition; SLP = speech-language pathologist; SMA = supplementary motor area; tDCS = transcranial direct current stimulation

# Introduction

You are about to introduce yourself to a new colleague. There are several people around you. Two people introduce themselves before you. You are sweating and your heart is racing. Then one. Now it is your turn. Your new colleague says, "Hi, I'm Bradley," and extends his hand. That is your cue. You know that in about a second, you are going to have to say your name, and you anticipate stuttering on your name. Then you stutter. Everybody is looking at you, which makes it harder for you to say your name. This is not a new experience for you, but it hurts every time.

This is a common experience for those who live with stuttering, a neurodevelopmental communication disorder that negatively impacts social, educational, and career opportunities for 70 million people worldwide. Little is known about the neural dynamics underlying stuttering events in real-life and consequential experiences as the one described in the example above. This is because most neural investigations of stuttering have focused on the fluent speech of stutterers (vs. control speakers), primarily due to the difficulty associated with eliciting stuttered speech in the unnatural environments of neuroimaging experiments. To address this challenge, we previously introduced a method to reliably elicit stuttered and fluent speech during neuroimaging[1], so that the brain bases of *stuttered speech* can be further elucidated.

Recent theoretical accounts of stuttering point to malfunction in the cortico-basal ganglia-thalamocortical (CBGTC) loop[2–4] ostensibly impeding the initiation and sequencing of speech motor programs. Several lines of investigation are consistent with this hypothesis. Anomalies have been found in stutterers in basal ganglia structure[5,6], activity[7–9], and connectivity with other key structures of the network such as the supplementary motor area (SMA).[4,10] Moreover, lesion studies[11], direct stimulation[12], and computational studies[3] suggest that these anomalies could lead to stuttering events. Increased beta desynchronization[13,14] and altered contingent negative variation[15] over precentral cortical regions in people who stutter can be viewed as support of the CBGTC hypothesis.

Importantly, the CBGTC account places differences in the neural dynamics underlying stuttered speech *at* speech initiation. Although malfunction at this level is plausible, there are data that suggest divergent neural dynamics (e.g., aberrant oscillatory activity) *prior* to speech initiation.[13,15–18] This widens the search space for the causes of stuttering to processes preceding speech initiation and is in line with reports from stutterers that they experience stuttering prior to overt disfluency.[19–21] However, there are several considerations with studies that focused on neural dynamics prior to speech initiation. Analyses were generally time-locked to speech onset (e.g., as determined by electromyographic activity or acoustic signal) or stimulus presentation. Speech onsets are difficult to identify reliably in instances of stuttered speech, such as inaudible prolongations (i.e., silent blocks), when the speaker *attempts* to initiate but there is no muscle activation or sound. Even if speech onsets could be determined reliably, not all neural events of interest prior to speech initiation will be time-locked to these onsets. Time-locking to a 'go' cue (a prompt to speak) is also problematic due to temporal inconsistencies in initiating speech, irrespective of stuttering. On the other hand, time-locking to stimulus presentation (e.g., a written word or picture) can be informative[e.g., 17], but it can make it difficult to differentiate stimulus processing from neural dynamics potentially related to stuttered speech. Time-locking to stimulus presentation is useful when the focus is on the neural dynamics elicited by the stimuli themselves. For example, Jackson et al.[22] found elevated activation in the right dorsolateral prefrontal cortex (R-DLPFC) in response to anticipated words (i.e., words that are associated with more stuttering for the individual, such as one's own name). Other considerations with studies that have looked at activity prior to speech initiation include relatively small sample sizes (less than ten participants), limited numbers of stuttered trials (less than 20%)[16,18], and not comparing stuttered and fluent speech in stutterers.[13,17]

A recent article by Korzeczek et al.[23] attempted to address some of these limitations. Their design featured a cue prompting participants to prepare to speak followed by a pseudoword to produce in each trial, effectively separating general from speech-related motor preparation processes. Korzeczek et al.[23] reported increased beta power from midline electrodes in participants with severe vs. mild stuttering. Increased beta power was interpreted as a global inhibition response. Global motor inhibition is thought to interrupt ongoing motor programs (speech or other) and interfere with action sequencing via stopping[24]. Global motor inhibition has also been

hypothesized to lead to stuttering[25,26]. Although the existence of an aberrant stopping mechanism in response to the requirement to prepare to speak is plausible, Korzeczek et al. did not report differences between stuttered and fluent speech, and the increased beta power was only reported for responses prior to fluent speech. A possible explanation for this is the limited number of stuttered trials, which only reached a mean of 20% across participants. Additionally, the authors did not localize the source of this activity, although they suggested a right preSMA or inferior frontal gyrus origin, in line with the global inhibition hypothesis. Finally, the stimuli in the Korzeczek et al. study were pseudowords, which likely involves processes distinct from real words.

In this study, we aimed to test the hypothesis that global motor inhibition underlies stuttered speech[25,26]. To this end, we designed a paradigm to faithfully simulate stuttering events as they often happen in the real world. In an initial visit, we used a novel clinical interview to determine participant-specific anticipated words[1] to increase the probability that speech would be stuttered during MEG testing. During the MEG recordings, participants read each word and produced the word at a go signal, which was preceded by a cue indicating the upcoming go signal. This effectively simulated a real-life speaking situation, such as when stutterers introduce themselves as in the above example: The speaker knows the word they are about to say (e.g., their name), and are then given a cue that signals the impending requirement to speak (the interlocutor extending their hand and beginning to say their name, e.g., “Hi, I’m Jack”). A jitter between word presentation and the cue was included to separate stimulus processing and speech planning from activity following the pre-cue.

# Materials and methods

This study was approved by the Institutional Review Board at New York University. Written consent was obtained from all participants in accordance with the Declaration of Helsinki.

## Participants

Participants were recruited via the last author’s database of stutterers, a mass email from the National Stuttering Association, and word of mouth. Participants included 29 adults who stutter

(8 female), with a mean age of 30.1 (SD = 7.8). Stuttering diagnosis was made by the last author, a speech-language pathologist (SLP) with 14 years of experience and expertise in stuttering intervention. All participants also self-reported as a stutterer and exhibited three or more stuttering-like disfluencies[27] with temporally aligned physical concomitants (e.g., eye blinking, head movements) during a 5-10 minute conversation. The Stuttering Severity Index - 4th Edition (SSI-4)[28] was also administered, and all participants responded to three subjective severity questions via 5-pt. Likert scales: 1) How severe would you rate your stuttering?; 2) How severe would other people rate your stuttering?; 3) Overall, how much does stuttering impact your life? (1 = Mild, 5 = Severe). There were two visits. Visit 1 included diagnostic testing and a clinical interview to determine participant-specific stimuli, i.e., anticipated words – words likely to be stuttered – so that the likelihood of stuttering during MEG testing was increased. Visit 2 included MEG testing.

## Clinical Interview

The interview was adapted from Jackson et al.[1,22] In that study, both anticipated and unanticipated words were elicited from participants, which yielded a near equal distribution of stuttered and fluent speech during fNIRS recording. However, Jackson et al. [1,22] included interactive speech whereas the current study did not; the likelihood of stuttering during testing with face-to-face communication is higher. Therefore, we only elicited anticipated words in the current study to increase the probability of a near-balanced distribution of stuttered and fluent speech in the absence of face-to-face communication (i.e., in the shielded room while MEG data were recorded). The interview is fully described in Jackson et al.[1], but is also summarized here. Participants were initially asked if they anticipated stuttering; all participants confirmed that they did. Participants were then asked to identify words that they anticipate. Most participants identified at least a few words, though there was variability across participants (as in Jackson et al.[1]). Participants were also provided with a prompt (e.g., “What about your name?”). Words that were independently generated, or generated based on a prompt comprise *participant-generated* words. Participants were then asked about anticipated sounds, i.e., word initial sounds that are problematic, which were used to create additional words beginning with these sounds (*researcher-generated* words). This was done ultimately to produce a list of 50 different, participant-specific words to be presented during MEG testing (visit 2).

## Stimuli

Each participant had their own list of 50 anticipated words, which were presented during MEG recording. Within this list, there were participant-generated words and researcher-generated words. Researcher-generated words were five syllables in length, because longer words tend to be stuttered more than shorter words.[29] The researcher-generated words started with the sounds identified by participants as anticipated, and the word list was developed using an online word generator. For example, if /b/ was identified as an anticipated sound, words like *biochemistry*, *biological*, and *biographical* may have been included. Participant-generated words were typically shorter than researcher-generated words. Participant-generated words presumably reflect an increased level of anticipation in that these words were verified by participants as being anticipated. Researcher-generated words may or may not have been anticipated *words* by participants, albeit there was likely some anticipation due to the sound itself.[1]

## Task

The behavioral task is depicted in Fig. 1. Each trial began with a fixation cross (baseline period) of variable duration (1 – 1.5 sec). A word from the anticipated words list (see Stimuli section) appeared in the center of the screen (0.4 sec) followed by a blank screen of variable duration (0.4 – 0.8 sec). After this blank screen, there was either a *speak* trial or a *catch* trial. For speak trials, a white asterisk appeared (henceforth, cue), signaling the requirement to speak the word on the following green asterisk (henceforth, go-signal). The duration of the white asterisk was 0.2 seconds and was always followed by 0.8 seconds of blank screen. The time between the onsets of the white asterisk (cue) and the green asterisk (go signal) was therefore always 1 second. The duration of the green asterisk on the screen was 0.5 seconds and was followed by a variable blank period (2 – 3 sec) to allow the participant to speak the word. The word STOP appeared at the end of this blank period at which point participants were requested to abort any incomplete speech acts and prepare for the next trial by remaining as still as possible. Catch trials (15% of trials) were introduced as a means to create uncertainty about the requirement to speak the anticipated word. In these catch trials, a red asterisk followed the blank screen and the participant was required to remain silent and await the following trial (Fig. 1). The overall design thus mirrored a common experience of people who stutter when the need to produce an anticipated word (e.g., one's own name) may be highly expected (e.g., when meeting new people) and

expected to happen upon request (cue; What is your name? And handshake prompt). The critical window for analysis was the cue period of 1 sec before the go signal (i.e., between the white and the green asterisks). The task consisted of seven blocks; each block included the list of 50 words presented in randomized order, for a total of 350 words per MEG session. Participants' faces were video recorded during the experiment.

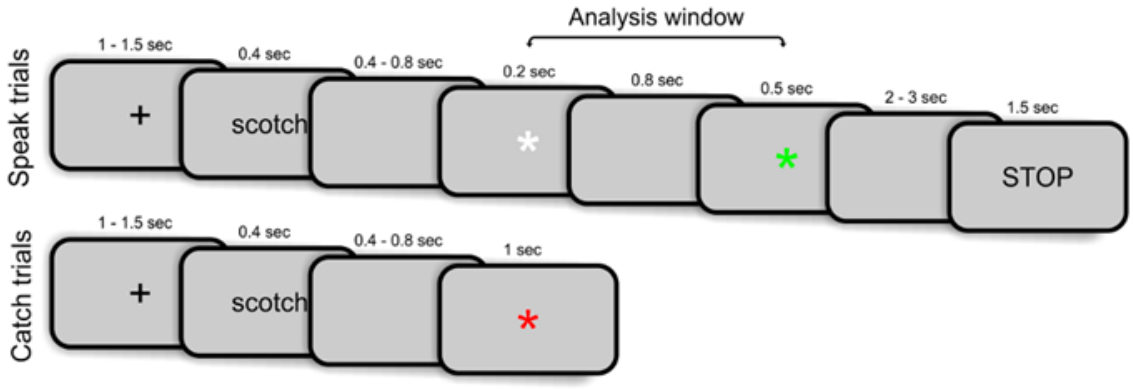


**Fig 1. Behavioral task.** Each trial began with a fixation cross of variable duration (Baseline period). Stimulus words appeared in the center of the screen followed by a blank screen of variable duration. For speak trials, a white asterisk appeared (cue), signaling the requirement to speak the word on the following green asterisk (go signal). Participants had 2 – 3 s to produce the words. Catch trials started in the same manner, however, a red asterisk appeared after the initial blank screen, indicating that participants should remain silent until the next trial.

## MEG data acquisition and preprocessing

Neuromagnetic responses were acquired using a 157-channel whole-head axial gradiometer (Kanazawa Institute of Technology, Japan) situated in a magnetically shielded room, with a sampling rate of 1000Hz. To monitor head position during the recordings, five electromagnetic coils were attached to the subject's head. We registered the location of these coils with respect to the MEG sensors before and after each block of the experiment. Participants' head shape was digitized immediately before the MEG recordings using a Polhemus digitizer and 3D digitizer software (Source Signal Imaging) along with 5 fiducial points, to align the position of the coils with participants' head shape, and 3 anatomical landmarks (nasion, and bilateral tragus), to further allow for the co-registration of participant's MEG data with an anatomical MRI template. An online band-pass filter (1Hz-200Hz) was applied to all MEG recordings.

Data preprocessing was conducted using custom Python scripts and MNE-python software.[30] Bad channels were first selected and interpolated using spherical spline interpolation. A least-squares projection was then fitted to the data from a 2-minute empty room recording acquired at the beginning of each MEG session and the corresponding component was removed. MEG signals were next digitally low-pass filtered at 50Hz using MNE-python's default parameters with firwin design and finally epoched between -2700ms and 500ms relative to the onset of presentation of the go signal (green asterisk; Fig. 1). Linear detrending was applied to the epochs to account for signal drift. Baseline correction was applied at the analysis phase (see below). An independent component analysis was used to correct for cardiac, ocular, and muscle artifacts. The epochs resulting from these steps were visually inspected and remaining artifactual trials were discarded from further analysis.

## Data Analysis - Behavioral

Trials were judged to be stuttered, fluent, or errors by the last author, an SLP with 14 years of experience and expertise in stuttering intervention. Stuttered trials were those with stuttering-like disfluencies including blocks, prolongations, or part-word repetitions. Error trials were those in which participants forgot or did not attempt to produce the target word. A generalized linear mixed model fit by maximum likelihood (family = binomial) in R[31] was used to assess variables that contributed to stuttered speech. Fixed factors included stimulus (participant- or researcher-generated), word length (number of letters), initial phoneme (consonant or vowel), and trial number, and participant was a random factor.

## Data Analysis - MEG

### *Time-frequency analysis in sensor space*

To determine differences in beta power between stuttered and fluent trials, we conducted a time-frequency analysis. Prior to the decomposition, trial types were equalized in counts. For the decomposition, we used a Stockwell transform[32] with a Gaussian window of width = 0.5, which offers a good balance between temporal and frequency resolution. The decomposition was performed for each condition separately (*stuttered*, *fluent*), for frequencies between 12 and 30 Hz

(beta frequency band) and times between the cue presentation and the presentation of the go signal (Fig. 1). A baseline correction was applied at this stage by subtracting the mean of the values between -1.6 and -1.3 prior to the cue presentation (i.e., within the baseline period; Fig. 1) followed by dividing by the mean of the same values (i.e., yielding percent change from baseline). Note that due to the jitter following word presentation, the baseline period differed for each trial. The contrast between *stuttered* and *fluent* trials was performed by direct subtraction (*stuttered* minus *fluent*) within participant before averaging the resulting difference across participants. To determine the statistical significance of observed differences, we first entered the difference data for each participant into a cluster-based permutation test (two-tailed; 1000 permutations) across participants (N = 29) with an initial *t*-threshold of 2.05 (equivalent to $p < 0.05$ for the number of participants) and a subsequent cluster threshold of $p < 0.05$. The same analysis was performed to determine differences in the theta (4 - 8 Hz), alpha (9 - 12 Hz), and low gamma (30 - 50 Hz) bands during the same time window (cue presentation to go signal).

Having established the existence of significant differences between the conditions by this approach in the beta band and to confirm statistical significance in a more restricted frequency and time range[33], we entered the participants' data, averaged between 22 and 27 Hz and between 0.2 and 0.5 seconds relative to cue onset, into a one-sample *t*-test (one-tailed). This range was estimated based on visual inspection of the time-frequency plot. Statistical significance was established by a threshold of $p < 0.05$.

### Correlation between overall beta power and stuttering severity

Spearman's Rank correlation coefficient was used to evaluate the relationship between the normalized beta power difference between stuttered and fluent trials across sensors and stuttering severity. Specifically, we used participants' beta power difference between stuttered and fluent trials within the specified times and frequency range (0.2 and 0.5 seconds, 22 to 27 Hz) and their SSI-4 score. One participant had missing data for the SSI-4, and was excluded from this analysis. Statistical significance was established by a threshold of $p < 0.05$. We identified an outlier in the data by a criterion of 2 SD from the mean of the SSI-4 scores. Results in-text are reported without the outlier and both with and without the outlier.

Correlations were also evaluated between participants' SSI-4 score and beta power relative to baseline in stuttered and fluent trials separately. Statistical significance was established by a threshold of $p < 0.05$.

### Power-spectral density in source space

To determine the cortical origins of observed power differences between *stuttered* and *fluent* trials, we projected each participant's epoched data to an *fsaverage* source space template (ICO 4). For each participant, we computed a forward model based on a 1-layer boundary element model and a minimum-norm inverse model (signal-to-noise ratio = 2; loose dipole fitting = 0.2, normal orientation) using a noise covariance matrix computed from all sensors averaged over a baseline period of 300 ms across trials and determined based on a log-likelihood and cross-validation procedure[34]. This inverse model was applied to the participant's epochs (*stuttered* and *fluent* separately, equalized in counts) using dynamic statistical parameter mapping (dSPM). Power spectral density in source space was estimated for each trial of each condition and using a multi-taper method. A slightly larger time-window than the time-frequency analysis (0.1 to 0.5 seconds after the cue) was used for a better estimation of power; the frequency range was kept to 22 to 27 Hz. We computed the average across trials for each condition from which the normalized difference in power [(*stuttered* – *fluent)* / (*stuttered* + *fluent*)] was estimated. Each participant's data was then morphed to a common template and entered into a cluster-based permutation test (one-tailed) across participants (N = 29) with an initial *t*-threshold equivalent to $p < 0.01$ and a subsequent cluster threshold of $p < 0.05$.

### Logistic regression analysis

We assessed the extent to which the trial-by-trial modulations of beta power in the R-preSMA, compared to baseline, predicted the corresponding trial's outcome (stuttered or fluent). For each participant and trial, we computed the normalized difference between the beta power (22 to 27 Hz) within R-preSMA in the identified times during the cue period (0.1 to 0.5 seconds) and in an equivalent 400ms period within the baseline (-1.6 to -1.2 seconds before the cue). These trial-wise power difference values were used to predict the outcome (stuttered or fluent) of the corresponding trials using logistic regression. Specifically, we fit and scored a logistic regression model per participant. Scores for each participant's model were determined based on the number

of correct predictions, such that if *j* outcomes are predicted correctly out of n observations (x values) the model's score is j/n. Participants' scores were then entered into a one-sample *t*-test against chance (0.5) to determine statistical significance across participants.

### Correlation between R-preSMA beta power and percent trials stuttered

Spearman's Rank correlation coefficient was used to evaluate the relationship between beta power with respect to baseline in the identified pre-SMA cluster and percent trials stuttered. To better characterize the relationship between these variables, we fit both a linear and an exponential regression model. Two outliers were identified as falling beyond the regression model's prediction interval. The $R^2$ of both linear and exponential models is reported with and without the effect of the outliers.

# Data availability

All data will be available in the paper's Supplementary Material upon acceptance.

# Results

## Behavioral

7,964 trials were included in the analysis. 3,166 trials (39.75%) were stuttered, 4,798 trials (60.25%) were fluent. Interrater reliability for 30% of the data set, between the final author and a SLP blind to the study, yielded a Cohen's weighted kappa of .93 ($p < .05$), indicating strong agreement.[35] Mean reaction time was 675.84 ms (SD = 272.99). Reaction time was calculated as the time between the go signal (i.e., the green asterisk) and speech onset as defined by the first articulatory movement or accessory behavior (as in Jackson et al.[22]) Accessory behaviors refer to non-speech behaviors that often co-occur with stuttering events (e.g., eye blinking, facial tension). Articulatory onset was defined as the first articulatory movement, which was determined based on visual inspection using Davinci Resolve (Black Magic Design, Australia). This allowed for frame-by-frame scanning (29.97 frames per second) of the recordings of participants' faces. Interrater reliability for 30% of the data set, between the last author and a SLP blind to the study, yielded a Cohen's weighted kappa of .85 ($p < .05$), indicating strong

agreement.[35] Due to the challenges associated with identifying anticipated words, there was significant variability across participants (M = 9.0; SD = 9.1). More stuttering was elicited for participant- vs. researcher-generated words ($\boldsymbol{\beta}$ = 0.24, z = 3.68, $p$ < .001). Table 1 includes percent trials stuttered, SSI-4 total scores and rating, responses to each subjective severity question (Q1-Q3), reaction time, and number of anticipated words identified by each participant (cf. words generated by the researchers based on anticipated sounds). Both word length and initial phoneme contributed to stuttered vs. fluent trials ($\boldsymbol{\beta}$ = -0.03, z = -5.04, $p$ < .001; $\boldsymbol{\beta}$ = -0.29, z = -5.63, $p$ < .001, respectively) such that longer words were stuttered *less frequently*, and words starting with consonants were stuttered more frequently than words starting with vowels. The word length finding is not in line with the literature[29], but this may be because participant-generated words were generally shorter than researcher-generated words. The initial phoneme result is in line with the literature.[36]

| ID | % Trials stuttered | SSI-4 total score | SSI-4 severity | Q1 | Q2 | Q3 | Reaction time (ms) | Anticipated words |
|---|---|---|---|---|---|---|---|---|
| 1607 | 46% | 22 | mild | 1.43 | 3.57 | 4.29 | 258.62 | 50 |
| 1609 | 63% | 30 | moderate | 3.57 | 3.57 | 2.86 | 289.65 | 12 |
| 1610 | 67% | 20 | mild | 0.71 | 0.71 | 1.43 | 383.42 | 14 |
| 1611 | 78% | 32 | severe | 4.29 | 3.57 | 2.14 | | 3 |
| 1613 | 22% | | | | | | 473.85 | |
| 1614 | 32% | 19 | mild | 2.14 | 2.86 | 3.57 | 240.26 | |
| 1615 | 48% | 31 | moderate | 2.14 | 2.86 | 4.29 | 737.81 | 3 |
| 1619 | 10% | 16 | very mild | 2.14 | 3.57 | 5.00 | | 8 |
| 1620 | 5% | 26 | moderate | 2.86 | 3.57 | 2.14 | | 4 |
| 1621 | 68% | 30 | moderate | 2.86 | 2.14 | 1.43 | | 1 |
| 1634 | 14% | 37 | very severe | | | | 700.10 | 2 |
| 1636 | 65% | 28 | moderate | 5 | 4 | 4 | 344.04 | 9 |
| 1637 | 7% | 19 | mild | 2 | 2 | 3 | 643.71 | 9 |
| 1675 | 50% | 35 | severe | 4 | 4 | 2 | 711.11 | 0 |
| 1678 | 3% | 10 | very mild | 2 | 3 | 2 | 448.16 | 8 |
| 1679 | 5% | 10 | very mild | 1 | 3 | 3 | 634.70 | 9 |
| 1681 | 6% | 13 | very mild | 1 | 1 | 2 | 390.76 | 14 |
| 1686 | 48% | 17 | very mild | 1 | 3 | 5 | 1071.84 | 6 |
| 1687 | 36% | 18 | mild | 3 | 4 | 5 | 833.58 | 9 |
| 1690 | 33% | 25 | moderate | 2 | 1 | 1 | 658.06 | 7 |
| 1695 | 44% | 9 | very mild | 3 | 3 | 2 | 764.17 | 3 |
| 1700 | 92% | 35 | severe | 3 | 4 | 4 | 1264.72 | 1 |
| 1705 | 44% | 18 | mild | 2 | 3 | 4 | 692.76 | 8 |
| 1709 | 48% | 11 | very mild | 3 | 3 | 2 | 686.09 | 15 |
| 1722 | 62% | 26 | moderate | 3 | 3 | 3 | 669.07 | 11 |
| 1733 | 50% | 19 | mild | 2 | 2 | 4 | 808.89 | 5 |
| 1734 | 25% | 34 | severe | 2 | 3 | 4 | 532.59 | 5 |
| 1736 | 31% | 13 | very mild | 2 | 3 | 3 | 1040.48 | 7 |
| 1737 | 6% | 15 | very mild | 3 | 4 | 3 | 893.65 | 19 |
| 1738 | 32% | 24 | mild | 3 | 3 | 3 | 1265.39 | 2 |
| 1742 | 32% | 19 | mild | 1 | 3 | 4 | 810.22 | 3 |

**Table 1. Behavioral data per participant.** Q1: How severe would you rate your stuttering?; Q2: How severe would other people rate your stuttering?; Q3: Overall, how much does stuttering impact your life? (1 = Mild, 5 = Severe). ms = milliseconds.

# Neural

## Time-frequency in sensor space

A cluster-based permutation test (N = 29, 1024 permutations; two-tailed) on the difference between stuttered and fluent trials (*Materials and methods*) indicated a significant difference in beta power ($p < 0.05$) with greater power in stuttered trials between 0.2 and 0.5 seconds after the cue and between 22 and 27 Hz (Fig. 2A). Following the suggestion of Sassenhagen and Draschkow[33], we entered participants' data averaged over these times and frequencies into a one-sample *t*-test to confirm this difference (*Materials and methods*). This analysis yielded a significant difference between the conditions ($t(28) = 2.96$, $p < 0.01$), with greater beta power in stuttered than fluent trials. No significant differences in power were found in the theta (4 - 8 Hz), alpha (9 - 12 Hz), or low gamma (30 - 50 Hz) bands.

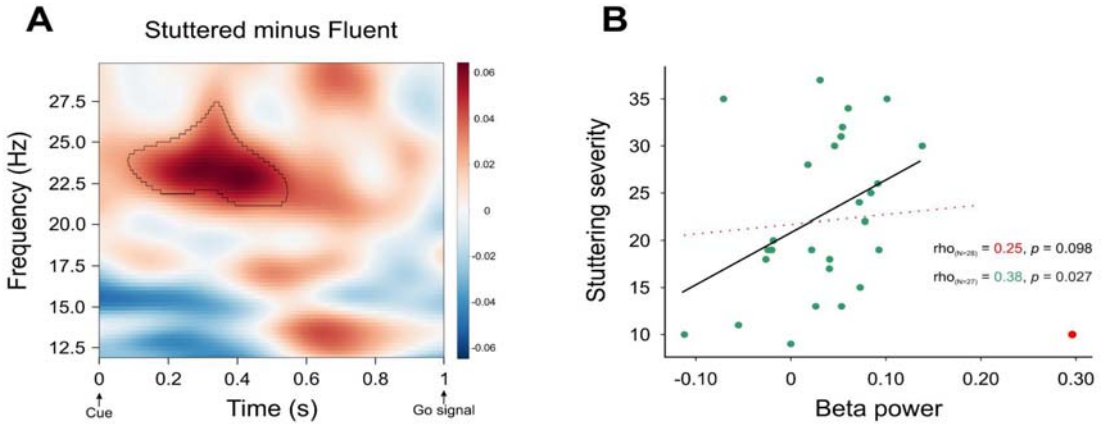


**Fig 2. Time frequency analysis. A. Greater beta power prior to stuttered compared to fluent speech.** The plot shows the difference (*stuttered* minus *fluent*) time-frequency plot with the significant cluster in the beta band highlighted (black contour). Significance was determined via a cluster-based permutation test ($p < 0.05$; two-tailed; 1000 permutations) across participants (N = 29). The time-frequency analysis window spanned 1 second between the cue (white asterisk; Fig. 1) and the go signal (green asterisk). Zero (0) is the time when the cue was presented while 1 is the time when the go-signal was presented. **B. Correlation between beta power and stuttering severity.** Scatterplot of the relationship between SSI-4 scores (a proxy for stuttering severity) and beta power (22 to 27 Hz,

0.2 to 0.5 seconds after the cue). Spearman rho values and corresponding p values reported in the plot for the correlation without (green) and with (red) the outlier (red dot at lower right).

We assessed the relationship between beta power differences within these times and frequency range (22 to 27 Hz, 0.2 to 0.5 seconds) and stuttering severity (indexed by SSI-4 scores). A significant correlation was found between beta power differences and stuttering severity (Spearman rho = 0.38, $p < 0.05$; Fig. 2B). No significant correlations were found between severity scores and beta power in either stuttered or fluent trials independently.

### Power-spectral density in source space

To determine the cortical origin of beta power differences between stuttered and fluent trials, we computed the normalized difference in power [(*stuttered – fluent)* / (*stuttered* + *fluent*)] from each participant's average power spectral density for each condition in source space (*Materials and methods*). A cluster-based permutation test (N = 29; 1000 permutations; one-tailed) across participants using participants' source projected data (the entire cortical surface morphed to a common fsaverage space) for times (0.1 to 0.5 seconds after the cue) and frequency range (22 to 27 Hz) (*Materials and methods)* yielded significant differences ($p < 0.05$) in a single cluster spanning the right anterior and medial SMA (i.e., preSMA; Fig 3). The precise location of the cluster in cortical space was determined by quantifying the number of sources in the cluster falling within each label of the Glasser et al.'s[37] cortical atlas. The largest number of sources fell into label 6ma (medial anterior) in the right hemisphere, corresponding to the R-preSMA. Zero sources fell into the right SMA proper (label 6mp [medial posterior]).

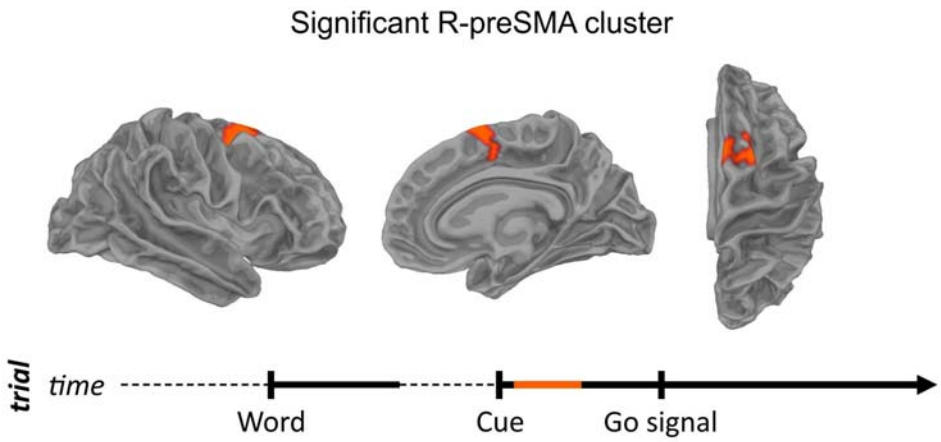


**Fig 3. Greater beta power in the R-preSMA prior to stuttered speech.** Significant cluster shown in a lateral (**left**), medial (**middle**), and axial (**right**) views. Significance was determined via a cluster-based permutation test across participants (one-tail) using each participant's power spectral density estimates in source space (5124 sources) averaged over frequencies 22 – 25 Hz and times 0.1 to 0.5 sec after the cue, with a *t*-threshold of $p < 0.01$ and a subsequent cluster threshold of $p < 0.05$. Timeline shows pertinent window of interest in orange.

### Relationship between R-preSMA power and stuttering outcome

These results, therefore, are in line with the hypothesis that stuttered speech elicits higher beta power *prior* to speech initiation in the R-preSMA, indicating a global inhibition response in reaction to the imminent requirement to speak an anticipated word.

Based on these results, we next evaluated the extent to which each subject's trial-by-trial beta power modulations in the R-preSMA, with respect to baseline, predicted the trial's outcome (fluent or stuttered). For each participant, we fit and scored a logistic regression model between the trial-wise beta power compared to baseline and the trials' outcome (*Materials and methods*). A one-sample *t*-test across subjects against chance (0.5) on the scores of each subject's logistic regression model indicated that the trial-by-trial beta power modulations relative to baseline predicted whether speech would be subsequently stuttered ($t(28) = 3.529$, $p < 0.001$).

We next assessed the relationship between beta power within the R-preSMA cluster and percentage of stuttered trials. We found a positive linear correlation between each participant's mean beta power across trials (relative to baseline; *Materials and methods*) and percent trials stuttered (Spearman rho = 0.5, $p < 0.01$; Fig. 4), indicating that enhanced beta power in the R-

preSMA leads to more stuttering. The superior fit of an exponential regression model ($R^2$ = 0.80) over a linear regression model ($R^2$ = 0.60) indicates that the percentage of trials stuttered increased exponentially with beta power increases in the R-preSMA with respect to baseline.

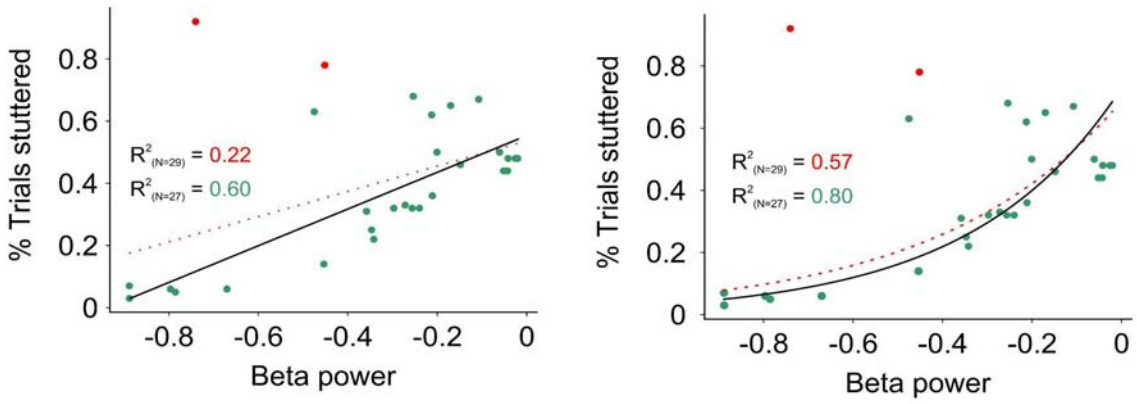


**Fig 4. R-preSMA beta power predicts the percentage of trials stuttered. Left:** Linear regression between beta power changes from baseline in the R-preSMA and percentage of trials stuttered. The plot shows a positive linear relationship both with (solid black line) and without (dotted red line) the 2 outliers (red dots; *Materials and methods*). **Right:** Exponential fit to the same data as the left plot, with (solid black line) and without (dotted red line) the outliers. The greater variance explained ($R^2$ values) for the exponential fit suggests that the percentage of trials stuttered grows exponentially with beta power increases from baseline.

In addition to the hypothesis-driven analyses discussed in this section, we conducted a whole-brain analysis of the differences between stuttered and fluent trials, for the interested reader (see *Whole brain event-related fields exploratory analysis* in Supplementary Material).

# Discussion

This study tested the hypothesis that global motor inhibition leads to stuttered speech. We simulated a real-life speaking situation in which the speaker knows the word they are about to say and is then given a cue signaling the impending requirement to speak. We leveraged a recently introduced clinical interview procedure[1] to elicit a relatively balanced number of stuttered and fluent trials, making this the largest and most balanced neurofunctional investigation of stuttered speech to date. Participants exhibited a neural response with characteristic signatures of global motor inhibition – enhanced beta power in the R-preSMA.[25]

Moreover, trial-by-trial beta power within the R-preSMA predicted subsequent stuttering. These findings have important theoretical and clinical implications in suggesting potential causes of stuttering prior to overt speech.

## Global Motor Inhibition Leads to Stuttering Events

The primary finding of this study is that, prior to speech initiation, stuttering is associated with increased beta power in the R-preSMA. Given its timing relative to the cue (~200-400 ms after) and its cortical origin, we interpret this modulation of beta oscillations as a global motor inhibition response to the imminent requirement to speak. This interpretation is consistent with the broader motor literature which shows that increases in beta power in the action-stopping network (including the R-preSMA) elicited by no-go cues trigger a global 'freeze' response.[24] It has been proposed that such freeze responses underlie stuttering by interfering with the initiation and sequencing of planned motor commands.[25,26] Only one study to date[i.e., 23] hypothesized global inhibition responses prior to speech initiation but differences between stuttered and fluent speech were not found. As previously mentioned, there are several possible reasons for this null finding, including a limited amount of stuttered speech and the use of pseudo-words, which have no social relevance and therefore are less likely to be stuttered.[19] In contrast to the approach of Korzeczek et al., we used anticipated words, which are meaningful to the participant and therefore more likely to be stuttered, even in the unnatural environment of a neuroimaging experiment.[1] Although Korzeczek et al. did not find differences between stuttered and fluent speech, or group differences between stutterers and non-stutterers, they did report an association between stuttering severity and beta power. Stutterers rated as more severe, based on pre-experiment clinical assessment, exhibited greater beta power. This is consistent with our result showing that stuttered speech is preceded by higher beta power than fluent speech, and also the observed relationship between beta power and stuttering severity.

## Global Motor Inhibition and Stuttering Anticipation

Because global motor inhibition precedes stuttered speech, it is necessary to discuss these findings in light of stuttering anticipation. Global inhibition and anticipation are separable but related processes that occur in similar time frames (i.e., prior to speech initiation). Elevated

activation in the right dorsolateral prefrontal cortex for anticipated versus unanticipated words has been interpreted as a substrate for error-likelihood monitoring[22], which could facilitate the speaker's responses to the anticipation of stuttering, for example, by substituting planned words, applying a learned strategy, or avoiding speech altogether.[19] Neef et al.[26] suggested that global inhibition is reactive, whereas anticipation is proactive. Reactive control involves the hyperdirect pathway (i.e., right preSMA and inferior frontal gyrus, subthalamic nucleus, and basal ganglia), whereas proactive control involves the right dorsolateral prefrontal cortex, caudate, and thalamus.[38] In line with our finding that level of anticipation (i.e., self- vs. researcher-identified) predicts overt stuttering responses, we propose that global inhibition results from anticipation, such that the associations between words and reactions to stuttering, triggers global motor inhibition. Future studies can assess how the relationship between anticipation and global motor inhibition contributes to the variability of stuttering events, i.e., the inconsistency with which stuttering occurs due to social-cognitive and linguistic factors.

## Initiation and Sequencing of Speech Motor Programs?

An alternative interpretation is that the reported beta power increases for stuttered speech in the preSMA reflect a malfunction in the CBGTC loop for speech.[2] Indeed, several studies reported atypical basal ganglia structure and activity as well as reduced connectivity between the basal ganglia and the SMA in stutterers compared to fluent speakers. This atypical neural activity has been hypothesized to cause stuttering by impeding the initiation or timely progression of motor commands, either because of the inability to integrate feedback regarding the current state within the planned sequence of movements[2] or because of the inability to properly time these movements.[39,40] We argue that these possibilities are unlikely for several reasons. First, in line with the functional dissociation between SMA proper and preSMA[41], these hypotheses generally relate to caudal parts of the SMA (i.e., SMA proper) instead of the preSMA. Second, our finding of enhanced beta power for stuttered trials is specific to the *right* preSMA, whereas accounts of speech sequencing and initiation involve the left SMA, as evidenced by recent meta-analyses.[42,43] Third, our analyses are time-locked to the cue rather than to speech onsets, which effectively dissociates our findings from speech initiation, given the temporal variability in actual speech onsets. Together with the times of the response (~200-400 ms after the cue), the reported increases in beta power are more likely to reflect responses to the cue. (Note that we similarly

aimed to dissociate cue responses from both motor preparation and stimulus processing by introducing a jittered interval between word presentation and cue.) The transient nature of the response as well as the timing precludes that the response in the right preSMA is due to the lateral readiness potential (LRP) or contingent negative variation (CNV), which are slow brain potential shifts.[44,45] Moreover, the LRP and CNV appear to be localized to SMA rather than preSMA.[44,45] Finally, regarding timing hypotheses, increases in cortical beta are thought to reflect compensation for reduced subcortical (basal ganglia) beta.[40] The implication is that enhanced beta power should reduce stuttering, which is the opposite of what we observed.

## Clinical Implications

The current findings, as well as other recent work[22], have important implications for neuromodulation as a possible component of stuttering therapy. Transcranial direct current stimulation (tDCS) is starting to be applied in stuttering research[46–48], albeit with modest results. For example, Garnett et al.[47] tested the impact of anodal tDCS on overt severity in 14 adult stutterers, and while they did not find significant effects on overt stuttering severity, they found that the atypically strong association between overt severity and right thalamocortical activity was attenuated after tDCS, especially in severe stutterers. It may be that the modest effects reported to date are due to an exclusive focus on the speech network. Future neuromodulation studies can target, for example, proactive (R-DLPFC) and reactive inhibition (R-preSMA) to test whether forward moving speech is facilitated by altering activation in these areas.

## Conclusion

We tested the hypothesis that stuttering events are preceded by global motor inhibition. We observed increased beta activity in the right preSMA, which is consistent with the global motor inhibition hypothesis. This suggests that when a speaker knows that they are going to have to produce a word, but before they initiate speech, global inhibition leads to stuttering events. This work addressed a significant challenge in stuttering research, i.e., eliciting a balanced amount of stuttered and fluent speech, so that the neural bases of stuttering events can be identified. These findings have potential clinical implications for neuromodulation, and also opens the door to new studies to further investigate the brain bases of stuttered speech.

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# Competing interests

The authors report no competing interests.

# Author contributions

Joan Orpella: Conceptualization: Lead; Formal Analysis: Lead; Investigation: Lead; Methodology: Lead; Writing: Lead. Graham Flick: Conceptualization: Equal; Formal Analysis: Supporting; Investigation: Equal; Methodology: Supporting; Writing: Supporting. M. Florencia Assaneo: Conceptualization: Equal; Formal Analysis: Supporting; Methodology: Supporting; Writing: Supporting. Liina Pylkkänen: Conceptualization: Supporting; Writing: Supporting. David Poeppel: Conceptualization: Supporting; Writing: Supporting. Eric S. Jackson: Conceptualization: Lead; Formal Analysis: Lead; Funding Acquisition: Lead; Investigation: Lead; Methodology: Lead; Project Administration: Lead; Writing: Lead.

# Supplementary material

Supplementary material is available at Brain online.

# Captions

**Fig 1. Behavioral task.** Each trial began with a fixation cross of variable duration (Baseline period). Stimulus words appeared in the center of the screen followed by a blank screen of variable duration. For speak trials, a white asterisk appeared (cue), signaling the requirement to speak the word on the following green asterisk (go signal). Participants had 2 – 3 s to produce

the words. Catch trials started in the same manner, however, a red asterisk appeared after the initial blank screen, indicating that participants should remain silent until the next trial.

**Fig 2. Time frequency analysis. A. Greater beta power prior to stuttered compared to fluent speech.** The plot shows the difference (*stuttered* minus *fluent*) time-frequency plot with the significant cluster in the beta band highlighted (black contour). Significance was determined via a cluster-based permutation test ($p < 0.05$; two-tailed; 1000 permutations) across participants (N = 29). The time-frequency analysis window spanned 1 second between the cue (white asterisk; Fig. 1 and the go signal (green asterisk). Zero (0) is the time when the cue was presented while 1 is the time when the go-signal was presented. **B. Correlation between beta power and stuttering severity.** Scatterplot of the relationship between SSI-4 scores (a proxy for stuttering severity) and beta power (22 to 27 Hz, 0.2 to 0.5 seconds after the cue). Spearman rho values and corresponding p values reported in the plot for the correlation without (green) and with (red) the outlier (red dot at lower right).

**Fig 3. Greater beta power in the R-preSMA prior to stuttered speech.** Significant cluster shown in a lateral (**left**), medial (**middle**), and axial (**right**) views. Significance was determined via a cluster-based permutation test across participants (one-tail) using each participant's power spectral density estimates in source space (5124 sources) averaged over frequencies 22 – 25 Hz and times 0.1 to 0.5 sec after the cue, with a *t*-threshold of $p < 0.01$ and a subsequent cluster threshold of $p < 0.05$. Timeline shows pertinent window of interest in orange.

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