Report

Current Biology

Stimulation of caudal inferior and middle frontal gyri disrupts planning during spoken interaction

Highlights

- Direct electrical stimulation was performed during an interactive speech task
- Perturbation of motor regions evoked articulation deficits
- Putative planning-related errors resulted from stimulating specific frontal sites
- Stimulation of different regions could increase or decrease response times

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In brief

Castellucci et al. find that direct electrical stimulation of the caudal inferior and middle frontal gyri during a question-answer task results in behavioral deficits consistent with disrupted planning, suggesting that these regions contain critical preparatory circuits engaged during spoken interaction.

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Stimulation of caudal inferior and middle frontal gyri disrupts planning during spoken interaction

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SUMMARY

Turn-taking is a central feature of conversation across languages and cultures.[1–4] This key social behavior requires numerous sensorimotor and cognitive operations[1,5,6] that can be organized into three general phases: comprehension of a partner's turn, preparation of a speaker's own turn, and execution of that turn. Using intracranial electrocorticography, we recently demonstrated that neural activity related to these phases is functionally distinct during turn-taking.[7] In particular, networks active during the perceptual and articulatory stages of turn-taking consisted of structures known to be important for speech-related sensory and motor processing,[8–17] while putative planning dynamics were most regularly observed in the caudal inferior frontal gyrus (cIFG) and the middle frontal gyrus (cMFG). To test if these structures are necessary for planning during spoken interaction, we used direct electrical stimulation (DES) to transiently perturb cortical function in neurosurgical patient-volunteers performing a question-answer task.[7,18,19] We found that stimulating the cIFG and cMFG led to various response errors[9,13,20,21] but not gross articulatory deficits, which instead resulted from DES of structures involved in motor control[8,13,20,22] (e.g., the precentral gyrus). Furthermore, perturbation of the cIFG and cMFG delayed inter-speaker timing—consistent with slowed planning—while faster responses could result from stimulation of sites located in other areas. Taken together, our findings suggest that the cIFG and cMFG contain critical preparatory circuits that are relevant for interactive language use.

RESULTS AND DISCUSSION

Given our research associating the cIFG and the cMFG with language-related planning,[7] we hypothesized that perturbation of these areas should result in behavioral deficits selectively related to preparing spoken output. In animal models, disruption of planning dynamics in premotor structures causes slower[23] and incorrect[24,25] non-vocal responses that are otherwise executed properly. Likewise, perturbations of white-matter tracts and cortical regions important for planning in humans can lead to slower and erroneous task-based speech.[26–31] For example, DES of the basal temporal language area (BTLA), a portion of the fusiform gyrus thought to be critical for semantic access during speech planning,[32–34] results in disrupted object naming.[27] We therefore predict that manipulation of the cIFG and cMFG should result in analogous deficits in the context of spoken interaction. Specifically, because these areas are persistently active early during planning,[7] we expect that disordering this activity would disturb high-level preparatory processes—such as formulating semantic structure or accessing lexical representations[35]—and thus lead to response errors but not articulatory dysfunction. Additionally, because efficient planning is central to achieving the rapid inter-speaker timing characteristic of conversational turn-taking,[1,18] we hypothesize that perturbing the cIFG and cMFG should disrupt this coordination by protracting preparation times.

Perturbation of neural activity during an interactive language task

To test our predictions, we used 50 Hz bipolar DES[8–14,20,26,27,34,36,37] to rapidly and reversibly perturb activity at 58 sites in 23 neurosurgical participants (Tables S1 and S2). We stimulated broadly across both cortical hemispheres (n = 48 in the left hemisphere) using both surface electrodes (n = 31) and intracerebral stereo-EEG depth electrodes (n = 27), enabling us to assess the behavioral results of disrupting our putative planning network (i.e., the cIFG and cMFG; n = 22 sites) as well as a range of additional cortical loci. Participants performed the critical information (CI) question-answer task,[18,19] which was also used in our electrocorticography study to isolate

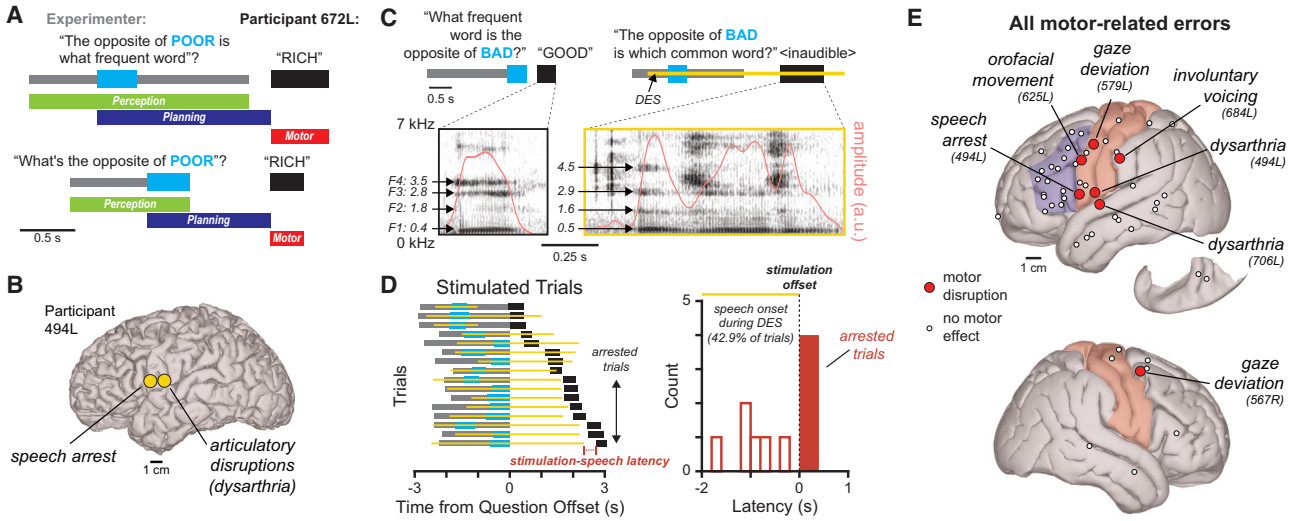

Figure 1. DES evokes motor deficits

(A) Example critical information (CI) questions where the CI is presented early (top) or late (bottom) with behavioral phases indicated.

(B) Left lateral cortical surface of participant 494L with two stimulation sites indicated.

(C) Example control trial (left) and trial where stimulation of the posterior site in (B) resulted in articulatory disruption (right); spectrograms of participant response with formant frequencies and envelope amplitude indicated (bottom).

(D) Schematics of all trials where the anterior site in (B) was stimulated (left) with latencies between stimulation and speech onset shown at right. See also Figure S1.

(E) Canonical cortical surface depicting all sites across participants where stimulation evoked motor deficits; all 6 stimulation sites within non-surface structures did not display motor disruptions (Table S2). The location of precentral and postcentral gyri is approximated in light red, and the regions of caudal inferior and middle frontal gyri displaying neural activity related to language planning[7] are approximated in light blue.

planning-related neural dynamics during interaction.[7] This paradigm relies on the same core processes as conversational turn-taking and requires speech perception, articulation, and all processes related to planning a one-word answer (e.g., conceptualization, lexical retrieval, and phonological encoding)[38,39] to occur in temporally defined epochs (Figure 1A). At each stimulation site, participants answered a verbally presented battery of 28 to 143 questions (65 ± 21; mean ± SD) as quickly as possible while DES was randomly delivered on approximately half of the trials (49 ± 3%; range: 42%–60%) (see STAR Methods). Stimulation intensity ranged from 7.5 V to 24 V (15 V ± 4 V) across sites, and DES was applied for 3.1 s ± 1.0 s during stimulated trials—corresponding to 85% ± 18% of total trial duration and 91% ± 3% of planning period duration. Our perturbations should therefore be capable of manipulating preparatory and sensorimotor processes related to spoken interaction.

Diverse motor deficits result from DES

We first observed that stimulation could elicit various motor disturbances that prevented performance of the CI task. For example, DES of two sites in participant 494L (Figure 1B) led to distinct deficits in articulation. Specifically, stimulation of a site in the subcentral gyrus, a region important for driving vocal tract movements,[10,17] resulted in unintelligible speech (i.e., dysarthria; Figure 1C). Stimulation of another site in the anterior precentral gyrus induced speech arrest, a well-documented DES-evoked motor deficit[10,13,14,20,21] proposed to arise from an inability to initiate articulation.[22] In support of this interpretation, we found that answer onset occurred only 76–390 ms (191 ms ± 124 ms) following stimulation offset on arrested trials (Figures 1D and S1), which is faster than single-word planning times[1,40] and thus suggests that DES at this site prevented the output of a pre-planned answer. We observed that stimulation evoked similar disruptions to overt action in 5 other participants (Figure 1E; Table S2), and sites exhibiting such effects were preferentially clustered to precentral and postcentral gyri[8,13,20,41–43] (actual: 86%, mean shuffled: 26% ± 16%; $p = 0.0007$) (permutation test, $n = 58$ electrodes). Our findings therefore indicate that these movement-related deficits resulted from selective perturbation of well-established motor networks located within these structures.[8–10,13,17]

DES can evoke putative planning errors

We next tested our first prediction that perturbing cIFG and cMFG would elicit non-motor response errors, which are traditionally employed in DES studies as an indicator of disrupted cognitive function during speech production.[9,13,20,21,27,34,36,44,45] We observed that DES often resulted in increased rates of semantic paraphasia (i.e., meaning-related errors; $n = 11$ sites) (Figure 2A), anomia (failure to generate a spoken answer; $n = 11$ sites) (Figure 2B), and hesitations (i.e., "um" and other disfluencies, see STAR Methods; $n = 22$ sites) (Figure 2C). Meanwhile, only a single site displayed an increased rate of neologisms (i.e., phonological errors) on stimulated trials (Table S2), and stimulation-induced errors did not exhibit gross articulatory disruptions (e.g., Figure 2A), suggesting that our perturbations likely did not affect late-stage operations related to motor control or programming phonological and phonetic structure.[35,38,46]

In our interactive paradigm, we observed that errors were typically infrequent at individual sites, and their occurrence was

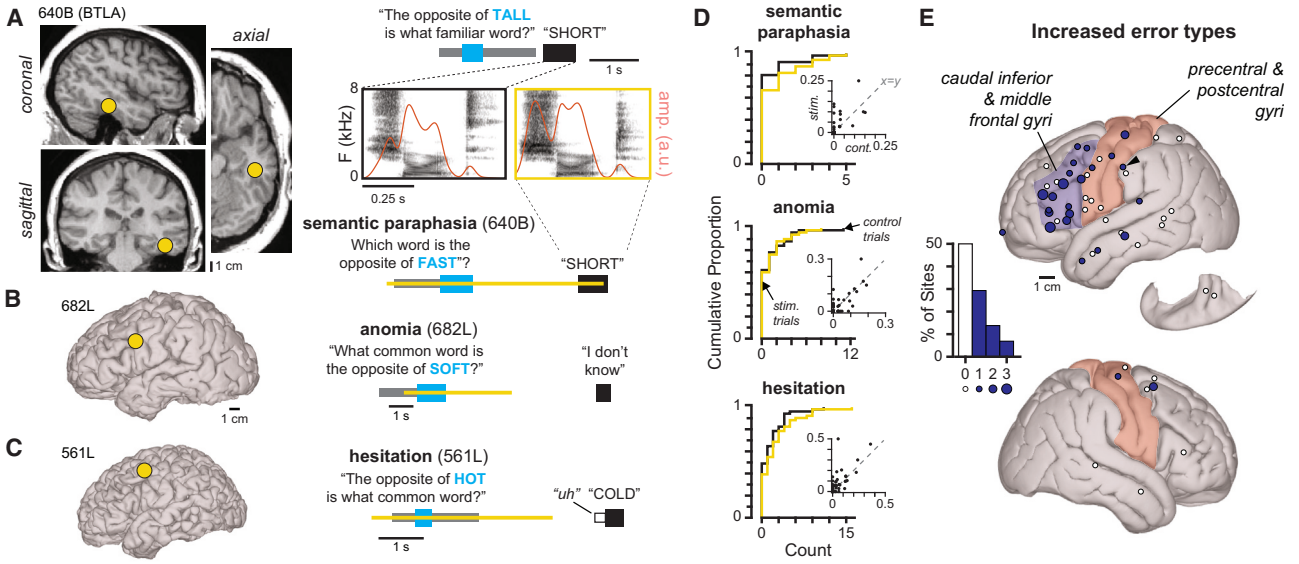

Figure 2. DES can elicit qualitative increases in the rate of putative planning-related errors

(A) Preoperative magnetic resonance images depicting the stimulation site within the basal temporal language area (BTLA). At right, example control trial (top) and trial where BTLA stimulation resulted in semantic paraphasia (bottom); spectrograms and envelope amplitude of example responses are also presented (middle).

(B and C) Example trials from sites where stimulation induced anomia (B) and hesitations (C); site locations indicated on participant cortical surfaces at left.

(D) Cumulative distribution functions of error counts in control and stimulated trials across sites; inset scatterplots depict error rates.

(E) Bar graph depicting the percentage of sites across participants where stimulation increased rates of one, two, or three error types (i.e., semantic paraphasia, anomia, or hesitations; in blue) or did not affect error rates (in white); the location of each site is shown on canonical cortical surfaces at right and its effect on error rates is indicated with colored circles. Arrow points to site displaying stimulation-induced neologisms. The location of precentral and postcentral gyri is approximated in light red, and the regions of caudal inferior and middle frontal gyri displaying neural activity related to language planning[7] are approximated in light blue. Stimulation of sites in non-surface structures led to increases in either three error types ($n = 1$; BTLA site), one error type ($n = 3$), or no error types ($n = 2$) (Table S2).

variable across sites (Figure 2D). Nevertheless, we found that stimulation qualitatively increased error rates within frontotemporal regions (Figure 2E; Table S2), consistent with past DES studies that observed a range of speech-related errors during non-interactive paradigms (e.g., picture naming, repetition).[9,13,20,21,47] For example, stimulating the BTLA[27,32–34] resulted in semantic errors, anomia, and hesitations (Figure 2A; Table S2). Aside from this site within the BTLA, we found that 54% of loci where stimulation increased rates of any error type were located in the cIFG (i.e., pars opercularis or pars triangularis) or the cMFG—which is significantly more than expected by chance (mean shuffled: 39% ± 7%; $p = 0.0219$) (permutation test, $n = 57$ electrodes). Therefore, while non-motor speech errors only sporadically resulted from DES, stimulation sites exhibiting qualitative increases in the occurrence of these deficits were preferentially located in the cIFG and the cMFG, consistent with our hypothesis that these regions are essential for language-related planning.

Inter-speaker timing can be modulated by DES

We next sought to test our second prediction that perturbation of planning-related neural activity would disrupt inter-speaker temporal coordination by protracting the time required to prepare an answer. In particular, conversational turn-taking exhibits rapid transitions between speakers, with inter-turn gaps (i.e., floor transfer offsets) regularly 200 ms in duration or less.[2,3] Achieving these latencies requires speakers to simultaneously plan responses while perceiving their partner's speech,[1,7,18] a behavioral strategy that is also possible when CI is presented early in the question (e.g., Figure 1A, top). During these early CI questions, participants typically responded to the experimenter following sub-second gaps that were significantly shorter than those observed in trials where the CI is presented late (Figure S2A), indicating that participants indeed began planning earlier when provided the opportunity. We therefore focused our analyses on early CI questions (see STAR Methods), and first tested how gap timing was modulated by DES of an established speech planning site (i.e., BTLA). We found that stimulation of the site within the BTLA (Figure 2A) significantly lengthened gaps (Figures 3A and 3B) ($p < 0.0001$; rank-sum test, $n = 44$ trials) without obviously affecting articulation (e.g., Figures 2A and 3A), indicating that perturbation of regions important for language-related planning can measurably disrupt inter-speaker timing.

Across all sites, we observed that stimulation could result in significantly longer gaps ($n = 9$; Figure 3C) or shorter gaps ($n = 4$ and 2 additional sites in late CI trials only; Figure 3D; Table S2), with the remaining sites leading to no measurable changes ($n = 34$; Figures 3E and S2B). Because DES could increase or decrease gap duration, we tested whether either type of timing alteration was associated with response errors (e.g., Figures 2A–2C). We found that all locations where stimulation lengthened gap duration also exhibited more anomia, semantic paraphasia, and/or hesitations in stimulated trials than

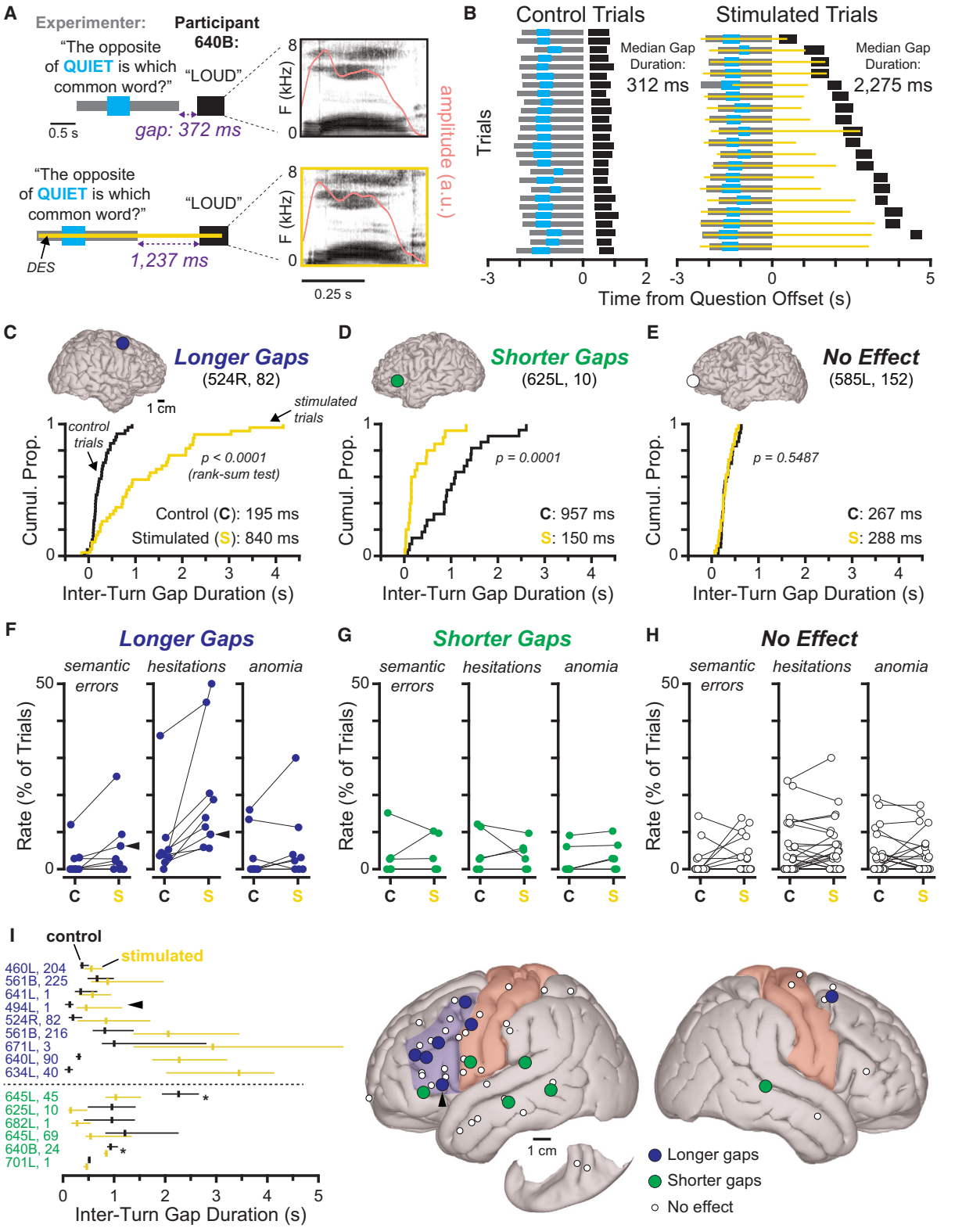

Figure 3. DES-induced modulations of inter-turn gap duration suggest distinct planning loci

(A) Example control trial (top left) and trial where the BTLA (see Figure 2A) was stimulated (bottom left) with inter-turn gap durations indicated; spectrograms of participant response with envelope amplitude overlaid (right).

(B) All trials related to stimulation of the site in (A) sorted by gap duration.

(legend continued on next page)

in control trials, with all such sites displaying an increase in at least one error type—significantly more than expected by chance (actual: 100%, mean shuffled: 48 ± 15%; $p = 0.0007$); conversely, a consistent trend for increased errors was not observed when stimulation resulted in shorter gaps (actual: 50%, mean shuffled: 48 ± 19%; $p = 0.6280$) or no effect in gap duration (actual: 44%, mean shuffled: 48 ± 5%; $p = 0.8511$) (permutation test, $n = 56$ electrodes) (Figures 3F–3H; Table S2). Therefore, perturbation of planning during speech production via DES is likely signaled by a combination of longer inter-turn gaps and qualitative behavioral deficits, including non-motor response errors. In support of this interpretation, we found that stimulation-induced changes in error rates are predictive of whether DES will significantly increase gap duration (χ^2 vs. constant model: 26.7; $p < 0.0001$) (logistic regression, $n = 48$ electrodes).

We then examined the anatomical distribution of stimulation sites across participants to test whether DES-induced modulations in gap duration were spatially organized. We found that sites where stimulation did not affect inter-turn gaps were located broadly across both hemispheres; in contrast, sites exhibiting stimulation-induced increases in gap duration were primarily restricted to the frontal cortex (Figure 3I). Excluding the site in the BTLA (Figure 2A), 7 of these 8 putative planning sites were located either in the cIFG or the cMFG—significantly more than expected if these sites were randomly distributed (actual: 88%, mean shuffled: 40 ± 16%; $p = 0.005$) (permutation test, $n = 55$ electrodes)—while a single site was located in the left posterior cingulate gyrus (Figure S2C; Table S2). Likewise, 32% of sites in the cIFG and cMFG displayed stimulation-induced increases in gap duration, while only 3% of sites outside these regions exhibited this deficit (shuffled mean: 15%). These results therefore confirm our second prediction that activity within the cIFG and cMFG is critical for maintaining rapid inter-speaker coordination. Meanwhile, sites where DES resulted in shorter gaps (Figure S3) were located outside the cIFG and cMFG and were not clustered to any specific cortical region (Figure 3I).

Finally, because we are the first to examine the effects of DES on inter-turn gaps, we tested whether the observed increases in gap duration could have result from factors other than perturbed planning. For example, participants in this study were undergoing surgical treatment for either epilepsy, brain tumors, Parkinson's disease, or essential tremor, and the constraints for these procedures required DES to be delivered using three different methods (Table S1). However, we found no significant relationship between (1) the probability of observing stimulation-induced gap lengthening and the clinical condition of the participant (χ^2 vs. constant model: 1.010, $p = 0.604$), (2) the type of stimulator used (χ^2 vs. constant model: 0.512, $p = 0.774$), or (3) stimulation intensity (χ^2 vs. constant model: 1.360, $p = 0.243$) (logistic regression, $n = 56$ electrodes), indicating that this putative planning deficit did not arise from these methodological differences. Increased inter-turn gap durations were also unlikely to have resulted from disrupted language comprehension, as perceptual deficits were observed at only a single stimulation site examined in this study (Figure S2D–S2H). Notably, DES of this locus in pars triangularis also evoked a combination of longer gaps, semantic paraphasia, and hesitations (arrows in Figures 3F–3I, S2G, and S2H), further suggesting a mixed function related to perception and planning.[7]

Conclusion

In summary, we confirm our predictions that perturbation of cIFG and cMFG would result in (1) non-articulatory response errors and (2) longer inter-speaker gaps in an interactive speech task. Our findings therefore suggest that these regions are essential to planning during spoken communication and provide additional evidence for the existence of a spatially and functionally distinct language-related planning network.[7] Previous studies have reported that DES of the left cIFG (i.e., classical Broca's region[48,49]) can result in a range of deficits related to cognitive (e.g., syntactic errors and semantic paraphasia) and motor (e.g., speech arrest and articulatory disruptions) function during speech production,[9,13,20–22,50] and activity within this area has been linked to multiple linguistic and domain-general operations, including phonological and phonetic encoding, action perception, working memory, and syntax/sequence processing.[46,48,51–62] Therefore, while the cIFG is likely a heterogeneous structure,[56,59] our results suggest that this region contains circuitry important for planning spoken language.[7]

This study highlights the importance of the cMFG for speech production, including in interactive contexts. Although regions of the cMFG are known to be important for several non-linguistic functions,[63–67] including eye movement (e.g., Figure 1E),[41,42] its role in language has remained unclear. A recent large-scale imaging study found that a subregion including the cMFG and adjacent precentral gyrus (i.e., Area 55b) displays activity during linguistic tasks and exhibits strong connectivity to language-associated networks.[68] Likewise, cMFG resection can lead to deficits in verbal fluency[69,70] and DES of the cMFG can result in speech arrest and various non-motor errors,[9,13,20,21,47,58] suggesting this area may contribute to spoken-language generation. Our stimulation results and intracranial recordings[7] further these important findings by demonstrating that cMFG perturbation elicits behavioral effects consistent with disrupted planning during speech production. While additional research is required to

(C–E) Cumulative distribution functions of gap duration for example sites where stimulation induced longer gaps (C), shorter gaps (D), or no statistical difference in gap duration (E); site location indicated on participant cortical surfaces at top.

(F–H) The error rates in control and stimulated trials for all sites where stimulation resulted in longer gaps (F), shorter gaps (G), or no effect on gap duration (H). For (F), the site which displayed stimulation-induced perceptual deficits (see Figure S2) is indicated with an arrow and was excluded from analyses of anomia.

(I) Median and interquartile range of gap duration for all sites where stimulation significantly affected this measure (left); sites where DES induced shorter gaps on late CI trials only indicated with asterisks. Participant and site number indicated in leftmost column (i.e., participant #, site #). At right, canonical cortical surfaces depicting the effect of stimulation on gap duration in all sites across participants; stimulation of sites in non-surface structures either lengthened gaps ($n = 2$; i.e., BTLA and posterior cingulate gyrus) or did not affect gap duration ($n = 4$) (Table S2). The location of precentral and postcentral gyri is approximated in light red, and the regions of the caudal inferior and middle frontal gyri displaying neural activity related to language planning[7] are approximated in light blue. The site that displayed stimulation-induced perceptual deficits (see Figure S2) is indicated with an arrow. See also Figure S3.

determine the specific operations[35,71,72] performed in the cMFG and to define the boundaries of its language-related territory, our current results as well as the proximity of the cMFG to speech areas in the cIFG,[68,73] the dorsal laryngeal motor cortex,[11,37] and the middle precentral gyrus[46] indicate this region is critical for language-related function.

Our broad sampling of the brain with DES and targeted measurement of inter-speaker timing revealed six sites where cortical stimulation resulted in significantly faster participant responses (Figure S3). Previous studies have reported that cortical perturbations can improve or speed up task behavior in humans and animal models, suggesting that this phenomenon is generalizable across species and behaviors.[74–76] We found that several sites outside of regions related to action and speech elicited faster responses; therefore, disrupting neural activity via DES may have modulated a variety of distinct processes both related and unrelated to language (e.g., global arousal, impulsivity, planning, and comprehension) that ultimately led to faster responses. While the underlying mechanisms remain unknown, these data provide promising initial evidence for cortical stimulation as a therapy for augmenting cognitive function, perhaps in a manner analogous to the usage of deep-brain stimulation and transcranial magnetic stimulation to treat motor and nonmotor symptoms in a range of disorders.[77–79]

This study advances our understanding of the human language network by providing causal evidence for the cIFG and the cMFG as critical planning areas. Our results suggest these regions contribute to generating the meaning of speech (e.g., conceptual or lexical content) rather than its lower-level structure (e.g., phonological or phonetic content), because perturbing these regions elicited both slower responses and high-level errors but not phonological or articulatory deficits. However, because the CI task requires multiple processes related to planning and task performance (e.g., planning of articulatory movements, semantic access, and selective attention), further experiments designed to behaviorally dissociate such processes are required to identify the precise planning operations performed within the cIFG and cMFG and assay the involvement of these regions in domain-general functions. For example, the longer interturn gaps caused by posterior cingulate stimulation (Figure S2C) may have resulted from disrupted cognitive control,[80,81] and similar roles have been suggested for subregions of the IFG.[51,56,57,59,82] Furthermore, the cIFG and cMFG likely operate within an extended planning network consisting of language-specific circuitry as well as areas involved in general task performance,[38,51,59,83,84] which is consistent with our finding that DES of many frontotemporal regions elicits putative planning-related errors (e.g., $n = 3$ sites in left middle temporal gyrus; see Figure 2E; Table S2). Nevertheless, our results demonstrate that DES combined with sensitive, ethologically relevant behavioral metrics is particularly well-suited to identifying planning loci and delineating their precise contributions to typical and disordered language generation.[85–87]

In conclusion, our recording and stimulation experiments provide strong support for a cortical planning system relevant for spoken communication that is centered on the cIFG and the cMFG. Recent studies have reported preparatory activity in frontal regions prior to volitional vocalization in non-human primates,[5,83,88–92] which may represent an evolutionary precursor to this human planning locus and thus provide a tractable model for its detailed circuit-level investigation.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cub.2024.04.080.

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AUTHOR CONTRIBUTIONS

Conceptualization, G.A.C. and M.A.L.; data curation, G.A.C., C.K.K., and F.T.; formal analysis, G.A.C., C.K.K., F.T., and D.C.; funding acquisition, J.D.W.G. and M.A.L.; investigation, G.A.C., D.C., and J.D.W.G.; methodology, G.A.C., C.K.K., F.T., D.C., M.A.L., and J.D.W.G.; project administration, G.A.C. and J.D.W.G.; resources, J.D.W.G. and M.A.L.; software, G.A.C., C.K.K., F.T., and D.C.; supervision, J.D.W.G. and M.A.L.; validation, G.A.C., C.K.K., and J.D.W.G.; visualization, G.A.C. and M.A.L.; writing – original draft, G.A.C.; writing – review & editing, G.A.C., C.K.K., F.T., D.C., J.D.W.G., and M.A.L.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
De-identified behavioral data	This paper	Open Science Framework; DOI: osf.io/6qubg
Software and algorithms		
MATLAB R2023a	Mathworks	https://www.mathworks.com/products/matlab.html
FreeSurfer	Massachusetts General Hospital, Harvard Medical School	http://surfer.nmr.mgh.harvard.edu/
FSL	University of Oxford	https://fsl.fmrib.ox.ac.uk/fsl/fslwiki
MRIcroGL	NeuroImaging Tools & Resources Collaboratory	https://www.nitrc.org/projects/mricrogl
Custom MATLAB code	This paper	Open Science Framework; doi: osf.io/6qubg
Other		
Data acquisition system	Neuralynx	ATLAS Neurophysiology System
Data acquisition system	Tucker-Davis Technologies	RZ2
Handheld bipolar stimulating probe	MVAP Medical Supplies	Magstim BiPolar Probe
Subdural electrocorticography electrodes	Ad-Tech	Intraoperative Monitoring Subdural Strip Electrodes; Epilepsy/LTM Subdural Grid Electrodes
Subdural stereo-EEG electrodes	Ad-Tech	Epilepsy/LTM Spencer Probe Depth Electrodes

RESOURCE AVAILABILITY

Lead contact

Requests for additional information and resources should be directed to the lead author, Michael A. Long (mlong@med.nyu.edu).

Materials availability

No new materials or reagents were generated for this study.

Data and code availability

Due to patient privacy concerns, de-identified behavioral data has been deposited on the Open Science Framework as of the publication date. Original MATLAB code used for analysis and figure generation is available on the Open Science Framework. DOIs are available in the key resources table. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY DETAILS

Ethics statement

All study participants consented to research, and the University of Iowa Institutional Review Board approved all procedures.

Study participants

Study participants were patient-volunteers undergoing surgical treatment at the University of Iowa Hospitals and Clinics for medically intractable epilepsy, brain tumors, or implantation of deep brain stimulation (DBS) electrodes. Data from participants with previous brain resections or infarcts were not included in this study. During the course of treatment, neural activity was recorded using electrocorticography (ECoG) electrodes and/or intracerebral stereo-EEG depth (sEEG) electrodes either chronically (i.e., seizure focus determination) or acutely (i.e., awake craniotomy for tumor removal/epilepsy treatment or during a deep-brain stimulation electrode implant procedure). In ten participants, language function was confirmed to be either left lateralized or bihemispherically distributed using Wada testing or functional magnetic resonance imaging; the remaining participants were right-handed (n = 11) or left-handed (n = 2) with unknown lateralization for language. Finally, all participants were native speakers of English except for one (684L); consequently, this participant was only screened for stimulation-induced sensorimotor effects and their behavioral data were not analyzed further. Additional demographic and clinical information is available in Table S1.

METHOD DETAILS

Data acquisition

For awake craniotomy patients, electrical signals resulting from direct electrical stimulation (DES) were recorded using subdural ECoG grids and/or strips manufactured by Ad-Tech Medical. Signals were amplified and sampled at 2034.5 Hz using a multichannel amplifier and digital acquisition system (PZ2 or PZ5 preamplifier with an RZ2 processer; Tucker-Davis Technologies). For chronically implanted epilepsy patients, electrical signals from subdural electrode grids, strips, or sEEG intracerebral depth electrodes (Ad-Tech) were recorded at 2000 Hz with a multichannel amplifier and digital acquisition system (Atlas system, Neuralynx). In both contexts, analog input channels synchronized with the neural recordings additionally acquired the output of 1-3 microphone(s) which captured the speech acoustics of the experimenter and participant. Input channels were typically sampled at 48,828 Hz by the TDT system and 16,000 Hz by the Neuralynx system and downsampled offline. In addition to the electrical signals, a video of the participant was also acquired at 24 fps for 20 of 23 experiments. The video was synced to the electrophysiological data after the experiment and provided a secondary high-quality audio recording channel, which was sampled at 48 kHz.

In a single awake craniotomy experiment, electrical signals were not recorded due to a recording system error and consequently only a video of the experiment was recorded (641L; see Table S1). This video provided images of the stimulator and captured experiment acoustics; thus, stimulation and behavioral timing was estimated using this data stream.

Direct electrical stimulation (DES)

DES was performed using a constant voltage stimulator (SD9, Grass Instruments). Charge balanced, biphasic pulses (0.2 ms duration) at 50 Hz were applied to the brain using either: 1) a handheld stimulator (Magstim BiPolar Probe; MVAP Medical Supplies, Inc., Thousand Oaks, CA) in awake craniotomy for tumor resection, 2) subdural ECoG strip electrodes (Ad-Tech) in awake craniotomies for deep brain stimulator implantation, or 3) subdural ECoG grid/strip electrodes or sEEG electrodes (Ad-Tech) in chronic epilepsy monitoring procedures. Because the position of the handheld stimulator could vary slightly from trial-to-trial (e.g., the stimulator could be removed momentarily to apply saline to the brain), we considered stimulation locations that varied by less than a centimeter to represent a single stimulation site. To titrate the stimulation voltage level, DES was first applied starting at ~5V and increased in ~2.5V steps until the participant reported a sensation, after-discharges were observed, or a maximum of 20-25V was reached. The highest voltage not resulting in a sensation or after-discharges was used as the stimulation level for the experiment. Occasionally, the stimulation voltage would be lowered during the course of an experiment if delayed after-discharges were observed. The stimulation voltage at each site included for analysis in this study is reported in Table S2; in cases where the voltage was lowered, the lowest intensity is reported.

Stimulation timing was manually controlled by the experimenter, who also presented the questions to the participant in most cases – however, in some experiments, a separate experimenters presented questions and delivered stimulation. The experimenter controlling the stimulator typically began applying DES prior to CI presentation and stopped when the participant spoke their response. However, considerable variability in stimulation timing was observed across trials, and any trial where DES was applied between CI offset and answer onset was considered a 'stimulated' trial. In all cases, participants were not given any sensory cues related to the timing of stimulation (e.g., visual or auditory).

Anatomical reconstructions

Cortical surface reconstruction was performed using T1-weighted or magnetization-prepared rapid gradient-echo (MPRAGE) images obtained during the clinical workup and the 'recon-all' pipeline in FreeSurfer.[93] In cases of poor T1 imaging, FreeSurfer processing was repeated with combined T1 and T2 images or T1 images with fluid-attenuated inversion recovery (FLAIR) sequences to improve pial surface parcellation. White-matter segmentation errors resulting from low image quality or tissue abnormalities were corrected manually.

Stimulation site localization in awake craniotomies for tumor resection

In one intraoperative tumor resection case (494L), stimulation site localization and coregistration was performed using intraoperative photographs, which were aligned to reconstructed cortical surface meshes via visual comparison of gyral anatomy by two raters (G.A.C. and J.D.W.G.). In all other cases, intraoperative photographs along with pre- and post-operative magnetic resonance (MR) images were used to localize both leads of the hand-held stimulator probe. Specifically, we first localized the craniotomy by 1) aligning intraoperative photographs to reconstructed cortical surfaces via visual inspection, 2) coregistering any burr holes and bone flap margins visible on the postoperative MR images to preoperative images using the FLIRT tool in the FSL package,[94] and 3) recording the coordinates from the Stealth neuro-navigation system (Medtronic, Minneapolis, MN, USA) used for craniotomy planning. Stimulation position was then defined on cortical surface renderings via visual comparison of gyral anatomy by two independent raters (F.T. and C.K.K.) and cross-verification with a third rater (J.D.W.G.).

Electrode localization in awake craniotomies for deep brain stimulator implantations

Localization of subdural ECoG strip electrodes (Ad-Tech, Racine, WI, USA) in patients undergoing deep brain stimulation (DBS) surgery was performed using a combination of intraoperative fluoroscopy, preoperative MR images, and pre- and post-implantation computed tomography (CT) collected for clinical reasons. Because the ECoG strips were temporarily placed during surgery and

removed before closure, intraoperative fluoroscopy was required to record strip locations for surface-based localization while CT and MR images were used to reconstruct cortical surfaces and align the fluoroscopic images. First, all MR and CT images were converted from Digital Imaging and Communications in Medicine (DICOM) to Neuroimaging Informatics Technology Initiative (NIfTI) format using dsm2niix tool in MRIcroGL.[95] Preoperative CT scans were then employed as a 3D frame for the coregistration of 2D fluoroscopic images. Specifically, the 'isosurface' function in MATLAB was used to compute the surface geometry of the preoperative CT, and cortical surface meshes were then transformed into CT space. To coregister the fluoroscopic image, multiple common control points were identified in the CT volume and 2D fluoroscopic projection, including skull contours, the superior and inferior terminations of the frontal sinuses, the glabella, and screws of the stereotactic frame (CRW; Integra, Inc., Princeton, NJ). Because the view plane angle and field of view varied between fluorograms, control points were individualized based on the visible skull anatomy. For each individual, a minimum of four different control points were utilized. For cases with an insufficient number of plainly visible skull landmarks, a post-implantation CT which displayed DBS leads and burr hole covers was coregistered with the pre-implantation CT to provide an additional set of reference points. Next, an orthographic projection from the CT image space to the imaging plane of the fluoroscope was computed through constrained minimization of squared error between control points. This procedure yielded an orthogonal affine projection relating control points in CT space to those in the fluorograms. After this alignment, ECoG electrode locations were defined as the point at which a line orthogonal to the fluoroscopy-aligned view plane, passing through the electrode shadow visible in the fluorogram, intersected the cortical surface. Finally, the Right-Anterior-Superior (RAS) coordinates of each electrode were transferred to Montreal Neurological Institute (MNI) space.

Electrode localization in chronically implanted patients

Electrode localization in epilepsy patients undergoing chronic electrode implantation was performed by identifying characteristic metallic-induced susceptibility artifacts and punctuate radiodensities in post-implantation MR and CT images, respectively. Electrode coordinates were then transferred to pre-implantation images via linear image coregistration, followed by manually guided thin-plate spline warping to account for nonlinear imaging and structural distortions. Control points for warping were determined by visually identifying corresponding landmark coordinates in pre- and post-implantation imaging.

Stimulation site coregistration

All contact locations were first determined on cortical surface renderings in RAS coordinate space. Anatomical labeling of the electrodes was performed through surface-based coregistration and segmentation for each participant using the Desikan-Killiany-Tourville (DKT) atlas[96,97] as assigned by FreeSurfer.[98] After automatic parcellation, electrode locations relative to DKT atlas labels were visually inspected by two raters (G.A.C and J.D.W.G) and corrected if necessary. To provide a consistent operational boundary between rostral and caudal middle frontal gyrus in line with our previous research,[7] raters considered any stimulation sites posterior to the extension of the anterior horizontal ramus of the inferior frontal gyrus as within caudal middle frontal gyrus and those anterior to this boundary to be within rostral middle frontal gyrus. Finally, preoperative T1 images were non-linearly coregistered to an MNI-aligned template brain (CIT168 template)[99] using symmetric diffeomorphic registration in the ANTs toolbox.[100]

Stimulation sites on the lateral cortical surface and superior temporal plane in individual participants were rendered on coregistration plots (e.g., Figure 1E) by plotting the center of the two stimulation electrodes on the gyral surface of the MNI152 reference brain. The locations of sEEG stimulation sites were rendered on canonical and individual cortical surfaces by plotting the coregistered coordinates of the most superficial contact of the electrode shaft on the gyral surface of the MNI152 brain or the location where the shaft penetrated the gyral surface, respectively. SEEG stimulation sites located on the medial cortical surface, within insular cortex, or on the ventral cortical surface (i.e., "non-surface sites"; $n = 6$) were not rendered on coregistration plots. The coordinates for each pair of stimulated electrodes are reported in Table S2.

Behavioral task

Participants completed the Critical Information (CI) task, which required them to answer simple questions as quickly as possible. The CI questions were read by the experimenter and adapted from a stimulus set used in our previous work[7] that itself was adapted from an established Dutch stimulus set.[18,19] Each CI question contains a single word (i.e., the critical information) which is required to answer the question (Figure 1A). In most experiments, questions required participants to generate the antonym of common words; however, in a subset of experiments, questions could also ask about animal sounds or body parts.

Questions were presented either in randomized order or in pseudorandomized order to avoid repeating the same CI on subsequent trials. On approximately half of the trials, DES was applied. In most experiments, stimulated and control (i.e., non-stimulated) trials were balanced such that the same question would be presented twice – once as a control trial and once as a stimulated trial. However, because of clinical considerations (e.g., time constraints in the operating room or to avoid after-discharges), question order, stimulation status, and wording often deviated from the planned protocol. In addition, most participants completed a block of the CI questions prior to the stimulation experiment to familiarize them with the task; these data were not analyzed in the present study. In one participant (460L), other tasks (e.g., repeating syllables, pressing a button) were interleaved with trials of the CI task.

The audio acquired with the electrophysiological acquisition system and/or video camera was annotated and timestamped by a trained phonetician (G.A.C.) to determine the onsets and offsets of all experimenter questions, CI, and participant responses. All final timestamping was performed blind in regard to stimulation timing. Questions which could not be accurately timestamped due to background noise (e.g., clinical team talking in background, operating room door closing, medical instrument alerts) were excluded

from analysis. Likewise, any antonym question where the participant gave an answer using "not" and the CI (e.g., Question: The opposite of hungry is what word? Answer: Not hungry) were rejected to ensure participants performed the task by generating a lexical item rather than repeating the CI. Aside from correct answers, any of the following were noted.

(1) Semantic paraphasia: 1) an incorrect answer (i.e., giving a synonym when the question required an antonym or giving an answer unrelated semantically to the CI) to a question which was answered correctly at least once or 2) answers related semantically to the CI and/or correct response were considered errors if the same correct answer at least twice during the experiment. In both cases, an answer would be considered a semantic error if the participant spontaneously corrected their answer prior to completing the next trial, except when a participant offered additional correct responses.
(2) Phonological paraphasia: a neologism, or an unattested English word consisting of segments that are properly articulated at a gross level.
(3) Anomia: questions that the participant failed to answer or could not respond for any reason, except for trials where the participant either reported not being able to hear due to background noise or appeared to fall asleep, which were excluded from further analysis. The stimulation site in 494L where perceptual dysfunction was reported (Figure S2D) was excluded from all analyses of anomia.
(4) Hesitations: trials which the participant produced a hesitation (e.g., "uh", "um") or dysfluency (e.g., stuttering, repetition or prolongation of the first segment) prior to responding. In addition, because all CI questions could be answered with a single word, any answers where this word was preceded by filler words (e.g., Question: The opposite of small is which word? "Small … uh, large") were considered trials containing hesitations. However, note that the presence of filler words does not reflect participants answering the questions in full sentences. Although participants were not explicitly instructed to answer using a single word, participants did so on 99.6% of trials. The remaining 15 trials were answered with short phrases containing filled or silent pauses (e.g., Question: The opposite of quiet is what common word? Answer: "Quiet is … <silent pause> … loud."); these trials were therefore considered to contain hesitations.
(5) Qualitative results: any site where stimulation resulted in a motor effect (e.g., speech arrest, gaze deviation, dysarthria, etc.) as defined by a neurosurgeon (J.D.W.G.). Such effects were categorized as either 'speech motor' (i.e., speech arrest, orofacial tetanus, involuntary orofacial movement, sensation of orofacial movement, dysarthria) or 'gaze motor' (i.e., involuntary head and/or eye movement). Any site which resulted in a sensation or movement that indicated the delivery of DES to the participant was not included in behavioral analyses. Descriptions of all qualitative motor effects are provided in Table S2.

Finally, any site displaying a higher rate of semantic paraphasia, anomia, hesitations, and/or neologisms in stimulated versus control trials (minimum increase: 1%) was considered to display an increase in errors. Importantly, participants were never corrected after producing a response error to avoid potential order effects.

QUANTIFICATION AND STATISTICAL ANALYSIS

Details regarding behavioral measurements and statistical testing can be found below. Statistical details can be found in figure legends and Results section (e.g., statistical tests used, exact value of n, what n represents). Furthermore, all trial numbers used for statistical testing are reported in Table S2. Summary statistics are reported as mean ± one standard deviation unless otherwise noted. Normal distribution of data was not assumed. Outliers in the distribution of gap durations were identified using a procedure detailed in the following section. The number of outliers rejected for each experiment are reported in Table S2.

Behavioral analysis

Inter-turn gap duration was defined as the duration between question offset and answer onset (excluding any hesitations) and was computed for all trials where an answer was produced (i.e., trials without anomia). Stimulus-response latency, defined as the duration between stimulation offset and answer onset, was calculated for all stimulated trials.

Stimulation-induced differences in gap duration at each site were assessed for early and late CI trials separately because CI position significantly affects gap timing.[7,18,19] Statistical significance in gap duration between control and stimulated trials was determined by first rejecting outliers in the gap duration distributions for control early trials, control late trials, stimulated early trials, and stimulated late trials separately (i.e., any gaps greater than 2 interquartile ranges above the 75th percentile or less than 2 interquartile ranges below the 25th percentile) and then performing rank-sum tests ($\alpha = 0.05$) on the outlier-rejected gap duration distributions in control and stimulated trials (significance testing for early and late trials was performed separately). Behavioral analyses were not performed unless there were at least 8 answered stimulated and 8 answered control trials after outlier rejection. Due to restricted study times, we presented participants with more early trials than late trials (at an ~2:1 ratio); consequently, many sites did not have sufficient late trials for behavioral analysis. Trial numbers, gap duration summary statistics, and other behavioral data for each stimulation site is presented in Table S2. Finally, we did not perform statistical analyses of gap durations for any sites where the median gap duration in control and stimulated trials were negative (i.e., the median response timing corresponded to an interruption; $n = 2$ indicated in Table S2) because repeated interruptions suggested that the participant was not engaged in typical turn-taking.[2–4,18,101]

Statistical testing

All analyses, including permutation tests (100,000 iterations), were performed in MATLAB (Mathworks, Natick, MA) using custom scripts. Rank-sum tests were performed with the 'ranksum' function, correlation analyses were performed with the 'corr' function, and logistic regression was performed using generalized linear modelling ('fitglm' function; binomial distribution, logit linkage function, and maximum of 1000 iterations specified). For the four logistic regression analyses performed, the occurrence of stimulation-induced increases in gap duration was used as the categorical response variable and predictor variables were defined as follows.

(1) Error rates vs. increased gap duration: the change in error rates (i.e., semantic paraphasia, hesitations, and anomia) were used as continuous predictor variables.
(2) Stimulation intensity vs. increased gap duration: Stimulation voltage was used as a single continuous predictor variable.
(3) Clinical condition vs. increased gap duration: Stimulation sites were divided into three groups according to whether participants were being treated for epilepsy, a brain tumor, or essential tremor/Parkinson's disease (combined due to limited sample size) (Table S1). These groups were then used as categorical dummy variables, with the combined essential tremor/Parkinson's disease group designated as the reference category.
(4) Stimulator type vs. increased gap duration: Stimulation sites were divided into three groups according to whether DES was delivered via ECoG electrodes, a handheld stimulator, or sEEG electrodes. These groups were then used as categorical dummy variables, with the sEEG group designated as the reference category.