

## Functional Segregation of Cortical Regions Underlying Speech Timing and Articulation

### Highlights

- Focal cooling can rapidly and reversibly alter speaking behavior
- Cooling effects on speech were primarily restricted to the left hemisphere
- Focal cooling can dissociate between speech timing and quality regions
- Distinct cortical sites appear to underlie premotor sequencing and articulation

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### In Brief

Long et al. measured the impact of thermal manipulation of specific cortical sites on the performance of simple vocal sequences. Cooling Broca's region and the speech motor cortex revealed a clear functional dissociation by altering speech timing and quality, respectively.

# Functional Segregation of Cortical Regions Underlying Speech Timing and Articulation

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## SUMMARY

Spoken language is a central part of our everyday lives, but the precise roles that individual cortical regions play in the production of speech are often poorly understood. To address this issue, we focally lowered the temperature of distinct cortical regions in awake neurosurgical patients, and we relate this perturbation to changes in produced speech sequences. Using this method, we confirm that speech is highly lateralized, with the vast majority of behavioral effects seen on the left hemisphere. We then use this approach to demonstrate a clear functional dissociation between nearby cortical speech sites. Focal cooling of pars triangularis/pars opercularis (Broca's region) and the ventral portion of the precentral gyrus (speech motor cortex) resulted in the manipulation of speech timing and articulation, respectively. Our results support a class of models that have proposed distinct processing centers underlying motor sequencing and execution for speech.

## INTRODUCTION

The production of spoken language is a complex process relying upon a number of interacting brain regions (Cogan et al., 2014; Flinker et al., 2015; Guenther, 2016; Indefrey and Levelt, 2004; Price, 2010). Transcranial magnetic stimulation (Pascual-Leone et al., 1991) and focal electrical current administration (Ojemann et al., 1989; Penfield and Rasmussen, 1950) have demonstrated that two key cortical centers are necessary for speech production: pars opercularis and pars triangularis (henceforth referred to as Broca's region) within the left inferior frontal gyrus (IFG) and its downstream target in the precentral gyrus (speech motor cortex), but the relative contributions of these areas during speech remain elusive. While the ventral motor cortex is generally considered to control overt articulation (Bouchard et al., 2013; Guenther et al., 2006; Murphy

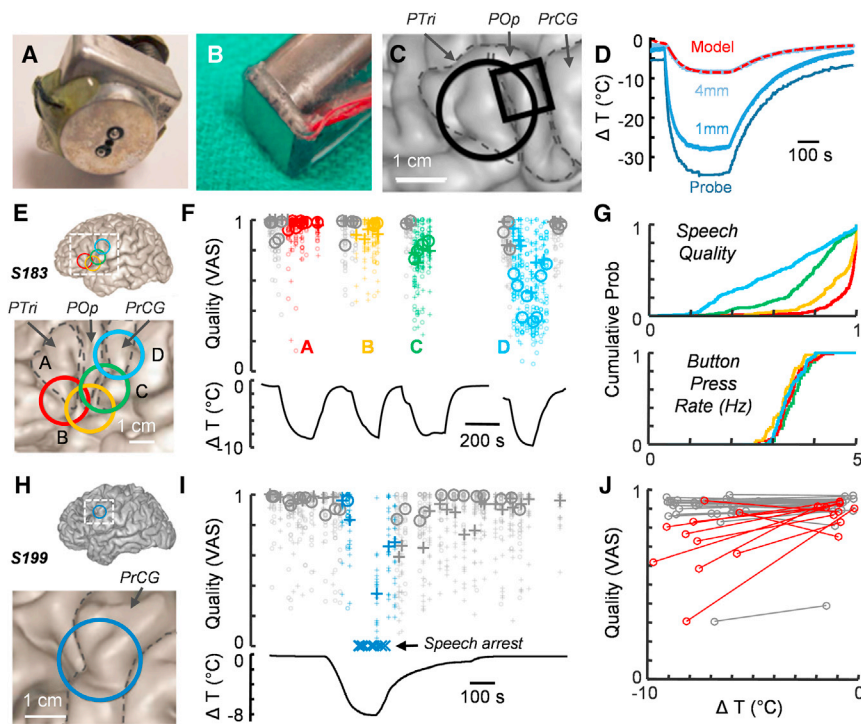
et al., 1997; Penfield and Boldrey, 1937), a large number of functional roles have been proposed for Broca's region (Flinker et al., 2015; Grodzinsky and Santi, 2008; Guenther, 2006; Haagoort, 2005; Hickok, 2012; Koechlin and Jubault, 2006; Musso et al., 2003; Price et al., 2011; Tettamanti and Weniger, 2006; Trupe et al., 2013), but few (if any) have been tested in a causal manner.

Here, we use focal cooling of specific brain regions during the performance of vocal sequences in order to measure the impact of this selective manipulation on different characteristics of produced speech. We find that our perturbation leads to a clear double dissociation (Gough et al., 2005; Lomber et al., 2010) in which speech quality and timing are differentially modified and regionally specific. Cooling the speech motor cortex leads to a striking decrease in speech quality, underscoring its role in articulation, while the same manipulation in Broca's region leads to consistent changes in speech rate. Our findings support the idea that Broca's region plays a key role in premotor sequencing and that specific speech-related movements are established within the primary motor cortex.

## RESULTS

### Cortical Cooling during Speech Production

To examine the roles that individual brain regions play in speech production, we investigated the impact of a focal manipulation on the timing and articulatory quality of spoken words. Since many neural properties are highly temperature dependent (Murphy et al., 1997; Sabatini and Regehr, 1996; Thompson et al., 1985; Volgushev et al., 2000a, 2000b), we reasoned that cortical cooling could transiently perturb circuit dynamics in the human brain, which is consistent with previous observations from simpler systems (Long and Fee, 2008; Pires and Hoy, 1992; Tang et al., 2010; Yamaguchi et al., 2008). We used two instruments to manipulate brain temperature which differed in their interface geometry (Figures 1A–1C) as well as the means by which cooling was achieved (see Experimental Procedures). We measured the spatiotemporal response to surface cooling (Figure 1D) (Smyth et al., 2015) in a sheep in order to estimate its effect on brain temperature at 4 mm, which roughly



**Figure 1. Focal Cooling Can Affect Speech Quality**

(A and B) The two cooling probe types used in this study. The brain interface can be either (A) circular (2-cm diameter) or (B) square (1 cm edge).

(C) An example reconstruction from S284 in which both cooling probe types were used. The footprints of the devices are marked in black. Gyri are identified as PTri (pars triangularis), POp (pars opercularis), and PrCG (precentral gyrus).

(D) Calibration curves for the circular cooling probe with measurements taken from within the body of the device and from additional points 1 mm and 4 mm under the surface of the probe. The dashed red trace represents the modeled temperature change at a depth of 4 mm (square probe:  $\delta = 1.5^\circ\text{C}$ ,  $\lambda = 2.5\text{mm}$ ,  $\tau = 28.3\text{ s}$ ; circular probe:  $\delta = 0^\circ\text{C}$ ,  $\lambda = 2.9\text{ mm}$ ,  $\tau = 29.3\text{ s}$ ; see [Experimental Procedures](#) for details).

(E) Cooling probe placements for S183.

(F) Changes in speech quality upon cooling corresponding to the four regions highlighted in (E). Pluses and circles represent the “counting” and “days of the week” tasks respectively. The small icons are quality scores from single listeners, and the large icons are the median values of quality scores for each vocalization across all listeners. The black curves below represent the estimated cortical temperature change.

(G) Cumulative probability histograms of individual quality scores (top) and button-press rates (bottom) for each of the cooling epochs in S183 with colors corresponding to (E).

(H) Cooling probe placement for S199.

(I) Quality degradation and speech arrest following cooling the location shown in (H) with the accompanying temperature changes shown below.

(J) A population plot from 38 cooling sites in 16 subjects showing average quality and estimated temperature changes during cooling compared with control (noncooled) values. The red lines indicate locations in which significant quality changes were observed ( $p < 0.001$ ,  $t$  test).

corresponds to the maximal depth of the gyral surface of human neocortex (Fischl and Dale, 2000).

We next used the cooling device in patient volunteers who were undergoing awake intracranial surgery for intractable epilepsy or brain tumor resection (Table 1). In total, 22 patients enrolled in the study, and sufficient data were collected from 16 of these individuals to allow for further analysis. The cooling probe was placed at various locations within the craniotomy. We cooled 42 total areas (one to seven cooling regions per subject) while subjects produced easily generated, over-learned vocal sequences, specifically, the days of the week (Monday through Friday) or a string of numbers (either 1–5 or 21–25). The majority of probe locations (61.9%) were aligned to language-critical sites identified with electrical stimulation-induced speech arrest (e.g., Figures 3A and S1). Cooling epochs lasted  $3.7 \pm 1.6$  min on average, and the maximum cooling level at a depth of 4 mm was estimated to be a decrease of  $6.6 \pm 1.3^\circ\text{C}$  relative to control values. As an aggregate, subjects produced a total of 783 word lists during cooling and 741 outside of cooling.

### Cooling Can Alter Articulatory Quality

In some cases, cortical cooling resulted in a transient degradation of speech performance that lasted for the duration of the manipulation (Figures 1E–1J; Movies S1 and S2). To quantify

the impact of cooling on speech quality for all recorded sound files, we used an online crowdsourcing approach adapted from a recently validated method (McAllister Byun et al., 2015), in which each vocalization was rated on a visual analog scale (VAS) (Munson et al., 2012) from 0 (extremely degraded) to 1 (typical/normal). Each subject’s sound files were evaluated by  $20.4 \pm 1.0$  online participants. Ratings were found to be reliable; scores were highly correlated within crowdsourced raters ( $r = 0.78$ ) and agreed with scores given by experienced listeners ( $r = 0.87$ ). In one example individual (S183), a cooling device was placed at four different sites (Figure 1E), resulting in a location-specific change in the quality of speech (Figures 1F and 1G). When location D was cooled, the quality score covaried with cortical temperature (Figure 1F), demonstrating that cooling was capable of degrading the quality of speech in a smoothly varying manner. Importantly, the cooling protocol applied to this subject did not affect another behavior (finger tapping) that required fine motor control of different muscle groups (Figures 1G and S2). In another subject (S199), focal cooling led to a temporary speech arrest that quickly resolved once the cortical temperature returned to baseline (Figures 1H and 1I). In contrast to electrical stimulation (Figure 3A), such cooling-related dysfluencies were relatively rare (see [Experimental Procedures](#) for complete list), occurring in 91 out of 1567 total prompts, and cooling-related vocal errors were only consistently induced

**Table 1. Patient Characteristics**

Number	Side Cooled	ID	Sex	Age (Years)	Diagnosis	Language Dominance	Handedness	Probe
1	L	183	F	39	epilepsy	L <sup>a</sup>	R	S
2	L	187	F	53	tumor	L	R	S
3	L	197	F	39	tumor	L	–	S
4	L	199	M	71	tumor	L	R	S
5	R	200	M	58	epilepsy	L	R	S
6	R	211	M	58	epilepsy	R <sup>a</sup>	L	P
7	L	234	F	50	tumor	L	R	P
8	L	239	F	33	tumor	L	R	P
9	L	244	M	63	tumor	L	L, R	P
10	R	246	M	41	epilepsy	L <sup>a</sup>	R	P
11	R	262	F	34	epilepsy	L <sup>a</sup>	L	P
12	L	279	F	59	tumor	L	R	P, S
13	L	284	M	41	epilepsy	L <sup>a</sup>	L	P, S
14	L	299	M	64	tumor	L	R	S
15	L	301	M	64	tumor	L	L	S
16	L	305	F	56	tumor	L	R	S

Demographics and experimental conditions of the 16 patients analyzed in this study.

<sup>a</sup>For language dominance, confirmation is indicated by the Wada test. In other conditions, stimulation was used to suggest hemispheric dominance. Handedness was also determined in 15 patients.

(Fisher's exact test,  $p < 0.01$ ) in two other locations (S187B – some incorrect responses; S279D – list truncation). Across the population of 16 subjects (Figure 1J), cooling resulted in significant quality changes in 25.6% (10 out of 39) of all locations analyzed.

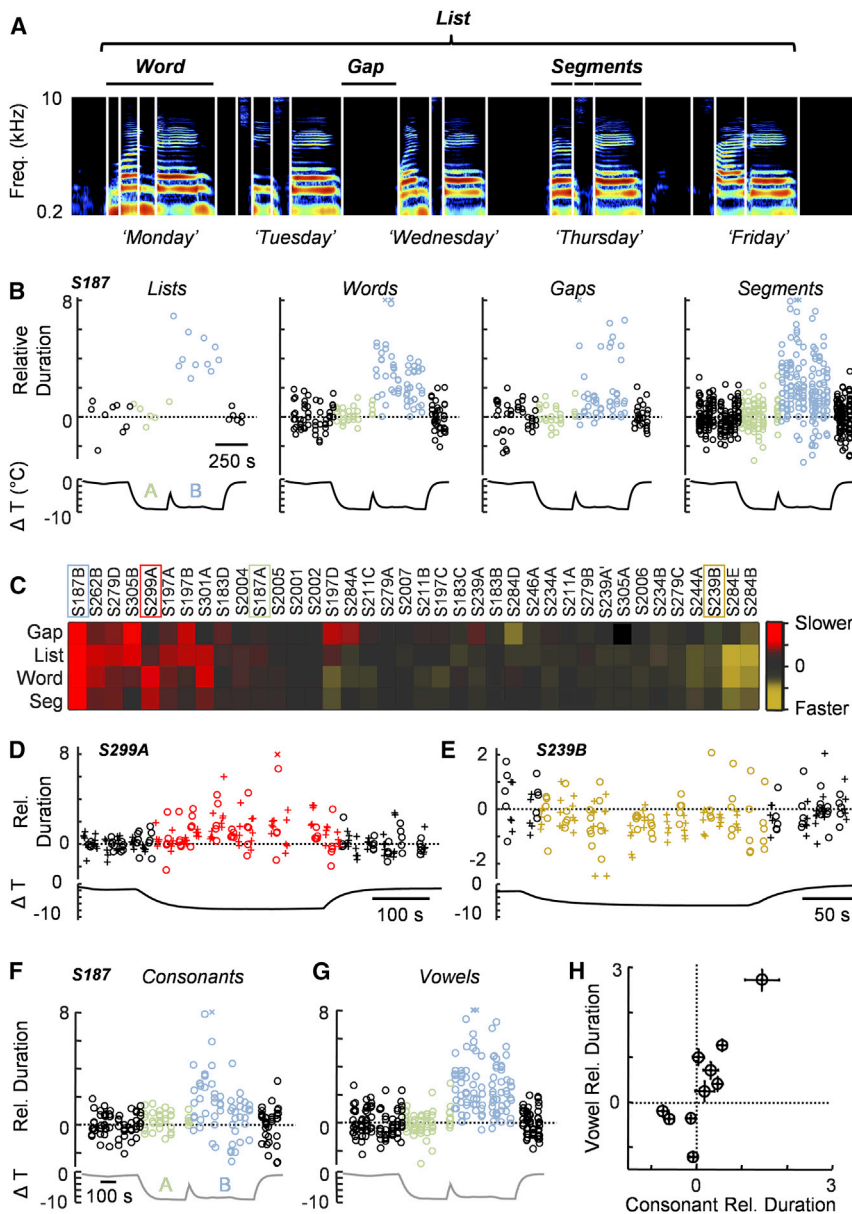
### Cooling Can Affect the Timing of Speech Elements

We then asked whether cooling the cortical surface would lead to changes in the timing of speech. We manually detected 29,387 reproducible spectrotemporal speech landmarks (mean and SD  $20.3 \pm 1.4$  and  $23.1 \pm 3.1$  landmarks per list for “days of the week” and “numbers,” respectively) in order to quantify the duration of different speech timescales (Figure 2A): lists, words, gaps, and segments. We compared the durations of each vocalization performed in cooled and control conditions (Figure 2) by normalizing to the mean and SD of controls for each vocal element (e.g., T in Tuesday) and then pooling across all vocalizations at that timescale (e.g., all segments). We also corrected for baseline drift (Figure S3); such instability may result from changes in attention or the level of previously administered conscious sedation. Identified speech elements could either expand (Figure 2D) or compress (Figure 2E) during cooling. Typically, all timescales that we measured covaried (Figures 2B and 2C; Movies S3 and S4), but occasionally, silent gaps would be affected differently than vocalizations (e.g., S197D). Across 16 subjects, 10 out of 39 cooling sites (25.6%) resulted in stretching of at least one timescale and 6 out of 39 (15.4%) exhibited compression, with 24 out of 39 (61.5%) resulting in no significant effects. Because selected segments were often composed of single phonemes or phonemes within an individual category, we examined whether cooling affected all of these elements equally. We identified 2,153 segments that could be collapsed into vowels ( $n = 978$ ) and consonants ( $n = 1175$ ) (Figures 2F–

2H), for 10 sites in which there was a significant change in segment duration, and we found that vowels showed a larger change relative to consonants ( $p < 0.0001$ , Wilcoxon rank-sum test; Figure 2H).

### Assembly of Functional Speech Maps

We next investigated whether the range of behavioral effects elicited by our manipulation could be partially explained based on the location of the cooling device. One major concern in this endeavor is that the gross anatomical morphology of frontal cortical structures can vary significantly across subjects (Brett et al., 2002), and therefore a simple transfer of the center coordinates (e.g., MNI locations) of the probe positions may not accurately represent the cooled area on a standardized brain map. To address this, we normalized all cooling locations onto an ICBM (International Consortium for Brain Mapping) template brain (Mazziotta et al., 2001) using nonlinear warping to conform to the brain's surface features (Figures S1 and S4; see Experimental Procedures), with 30 locations on the left hemisphere and 12 locations on the right hemisphere (Figure 3B). Each location could be labeled according to the primary behavioral effects elicited by cooling that site (Figures 3C and 3D). We then calculated the impact of our temperature manipulation on speech quality (Figure 1) and timing (Figure 2) within the canonical brain at high resolution. Each pixel (Figures S4E and S4F) was categorically assigned to be either “quality” or “timing” based on the relative values aggregated across cooling probes (Figure S5). In examining the resulting functional brain map (Figure 3E), we noticed a high degree of lateralization of both categories within Broca's region and speech motor cortex (see Experimental Procedures for precise locations on the ICBM brain). On the right hemisphere, only 14.2% of the total area tested was shown to result in measurable changes in speech, and these locations



**Figure 2. Focal Cooling Can Affect Speech Timing**

(A) A sonogram of the “days of the week” task with a logarithmic frequency axis.

(B) Cooling can lead to a significant increase in speech duration across multiple timescales. For S187, cooling location B (light blue, pars opercularis and precentral gyrus) resulted in significant stretching of lists, words, gaps, and segments (relative to their respective controls), whereas cooling location A (light green, dorsal inferior frontal gyrus) had a minimal effect. The X marks indicate values outside the range given by the ordinate.

(C) A population plot showing the effects of cooling on the duration of gaps, lists, words, and segments for 38 sites across 15 subjects. The location IDs of the examples shown elsewhere in (B), (D), and (E) are demarcated with boxes. Colors indicate cooling induced changes to the mean duration of vocal elements (colorbar at right). The measurement of gaps in region A of S305 was excluded from the dataset because of unstable baseline values.

(D and E) In some cases, cooling led to either a significant increase (D, pars opercularis and precentral gyrus) or decrease (E, pars opercularis) in the duration of words.

(F and G) The timing of all (F) consonants and (G) vowels is shown for S187.

(H) The change in duration of vowels versus that of consonants for the ten sites across eight patients with significant changes in the timing of identified vocal segments. Error bars represent the SEM.

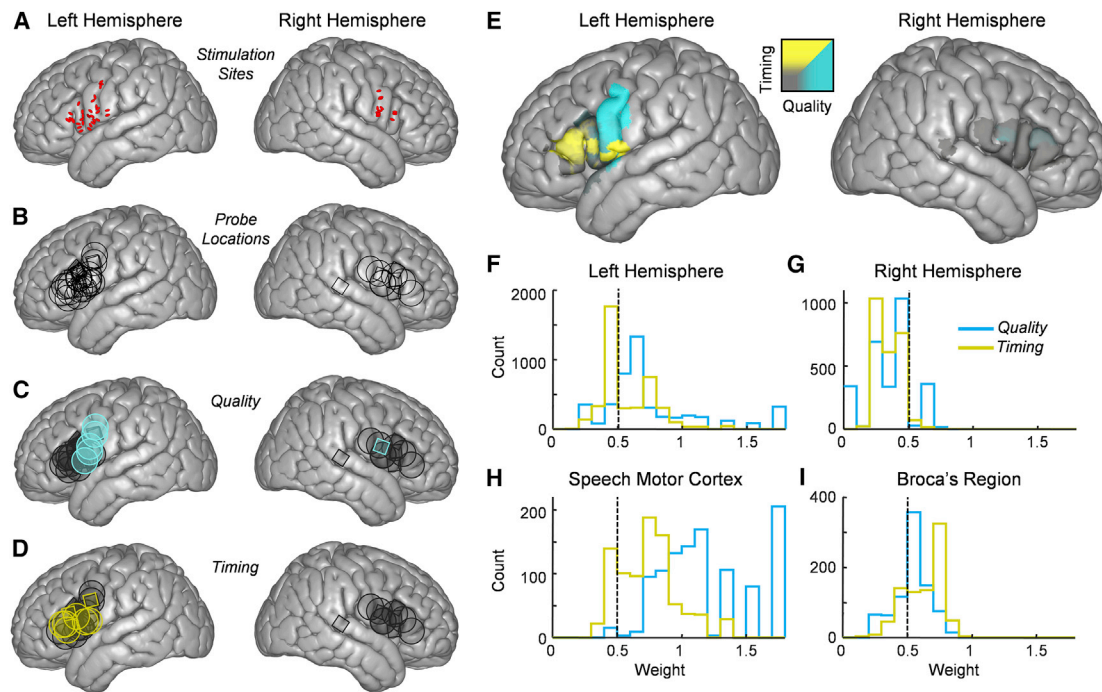
were all categorized as alterations in speech quality (Figures 3E and 3G). Conversely, focal cooling administered to the left hemisphere resulted in changes in 85.0% of the total area tested (28.5% timing and 56.5% quality) (Figures 3E and 3F). This effect was reflected in the magnitude of quality and timing across hemispheres ( $p < 0.0001$ , Wilcoxon rank-sum test). Because we interrogated the left hemisphere more completely than the right, we repeated this analysis excluding the dorsal portion of the precentral gyrus where coverage was insufficient on the right hemisphere. In this more restricted view, we continued to observe a highly significant lateralization effect ( $p < 0.0001$ , Wilcoxon rank-sum test).

In addition to a lateralization of speech-related cooling effects, we also investigated the nature of changes with respect to distinct cortical regions in the left hemisphere. When we exam-

ined the surface of the left speech motor cortex, we observed a significant cooling-induced change in speech quality. Specifically, 79.3% of the sites within this region resulted in quality changes compared with 19.3% of the sites that preferentially caused changes in speech timing and 1.3% having no significant effects (Figures 3E and 3H). In contrast, cooling Broca’s region had the opposite impact (Figures 3E and 3I), with 68.6% of the gyral surface resulting in timing changes, 15.1% causing quality changes, and 16.4% failing to elicit a significant effect. These disparities could also be seen at the level of the mean timing (T) and quality (Q) values averaged across the gyral surfaces (speech motor cortex:  $T = 0.74 \pm 0.23$ ,  $Q = 1.2 \pm 0.33$ ; Broca’s region:  $T = 0.62 \pm 0.15$ ,  $Q = 0.54 \pm 0.13$ ) ( $p < 0.0001$ , Wilcoxon rank-sum test). Additionally, in the cases where a timing effect could be seen in the speech motor cortex (Figures 3D and S5A), we noted that silent gaps were affected more strongly than words, whereas the reverse was true in Broca’s region ( $p < 0.0001$ , one-sided Wilcoxon signed rank test).

## DISCUSSION

We used focal cooling to manipulate cortical dynamics, allowing us to characterize the processing underlying various stages of



**Figure 3. Functional Speech Maps as Determined by Electrical Stimulation and Focal Cooling**

(A) Electrical stimulation mapping sites (represented by red ovals) that resulted in speech arrest for left (30 sites in 11 subjects) and right (12 sites in 4 subjects) hemispheres plotted on an ICBM template brain.  
 (B) Template brains on the left and right hemispheres displaying the cooling probe locations across all subjects on the left (30 sites in 12 subjects) and right (12 sites in 4 subjects) hemispheres.  
 (C and D) Cooling sites were designated to result in either a significant change in (C) speech quality or (D) timing, indicated by blue or yellow shapes, respectively. Sites that were significant for both timing and quality were designated as the category with the larger effect.  
 (E) A functional map showing behavioral results for both hemispheres.  
 (F and G) Histograms of all pixel values from speech areas on (F) left and (G) right hemispheres showing values for quality (blue) and timing (yellow).  
 (H and I) The distribution of timing and quality values for pixels in the (H) speech motor cortex and (I) Broca's region.

speech production. Although focal cooling is rarely performed in humans outside of the context of suppressing epileptic activity (Bakken et al., 2003; Brooks, 1983; Fisher, 2012; Karkar et al., 2002; Pásztor and Tomka, 1969; Smyth et al., 2015), we now demonstrate that this approach can be an effective method for localizing speech-related cortical sites. Importantly, cooling lacks many of the drawbacks of electrical stimulation mapping, such as the possibility of initiating a seizure during the procedure (Piccioni and Fanzio, 2008). Furthermore, we show that focal cooling can be used as a discovery tool to test hypotheses concerning cortical function.

Our first finding using this method is that, while we were able to observe instances of cooling-related effects bilaterally, we found that they were primarily confined to the left hemisphere. This lateralization is consistent with clinical observations (Damasio, 1992), but opposed to recently emerging views concerning the distributed nature of speech motor control (Cogan et al., 2014; Price, 2010). In one case included in our study (S211), we were unable to see a functional effect of cooling the right pars opercularis despite the fact that the subject exhibited right language dominance. Additional data are needed to understand the anatomical organization of speech production centers in these individuals.

Within the left hemisphere, we used cooling to demonstrate a clear functional dissociation (Gelfand and Bookheimer, 2003; Gough et al., 2005) between the speech motor cortex and Broca's region. Cooling the speech motor cortex leads to changes in the quality of vocalizations. Neurons within this area display an articulator-specific topographic organization (Bouchard et al., 2013) and directly contact the motor neurons that drive speech production muscles (Simonyan, 2014). Thus, the cooling-related speech dysarticulation highlights the impact of these neuronal populations on speech kinematics. In contrast, cooling Broca's area often led to changes in the speech rate. Computational models have proposed independent signals that can control the speed of movements (Bullock and Grossberg, 1988) including speech (Guenther, 1995, 2016), and our results are consistent with the hypothesis that this computation may involve the IFG. The IFG is a heterogeneous structure (Amunts and Zilles, 2012) with a number of subregions that may carry out distinct roles. For example, studies have found differences between the dorsal IFG and other nearby regions, such as the inferior frontal sulcus (Bohland and Guenther, 2006; Myers et al., 2009) or the ventral IFG (Papoutsis et al., 2009). In future experiments, we hope to further refine our technique to perturb individual cortical subregions in order to test these observations

and to unveil any additional functional organization that may exist within speech production areas.

The mechanisms by which the IFG may affect the rate of speech production are poorly understood. However, we can look for potential insight in simpler systems (Long and Fee, 2008; McKibben and Bass, 1998; Pires and Hoy, 1992; Yamaguchi et al., 2008), in which cooling premotor vocal circuits has also been shown to result in slowed vocalizations. In the songbird, a critical premotor structure forms fine-grained sequences of activity in which each participating neuron is active for a single moment (approximately 10 ms) during the vocalization (Hahnloser et al., 2002). Selective cooling of this region stretches the sequence and the resultant singing behavior (Long and Fee, 2008). Because the majority of temperature-related changes reported here also involved a decrease in speech rate, we propose the intriguing possibility that at least one affected sub-part of Broca's region is the site of sequence generation for speech production, a notion that is consistent with some previous findings (Clerget et al., 2011; Gelfand and Bookheimer, 2003; Uddén and Bahlmann, 2012). A range of relevant models can be directly addressed in future experiments using high-density recording techniques to measure activity at a fine spatial scale (Bouchard et al., 2013), and even at the single-neuron level (Fried et al., 2014), to better understand the nature of this local processing. By adopting a sequence generation framework, we can begin to understand the mechanisms by which premotor commands are represented in Broca's region and the processes enabling these commands to be associated with specific behavioral elements in downstream targets (Flinker et al., 2015; Lashley, 1951).

## EXPERIMENTAL PROCEDURES

For details on all methods, please see [Supplemental Information](#).

## SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, five figures, and four movies and can be found with this article online at <http://dx.doi.org/10.1016/j.neuron.2016.01.032>.

## AUTHOR CONTRIBUTIONS

M.A.L. and J.D.W.G. designed the research, and J.D.W.G., M.A.H., and M.A.L. collected data for the experiments. M.A.L. and K.A.K. wrote the paper. K.A.K. and M.A.L. were central to analyzing every aspect of the collected data and M.A.S., R.C.C., T.M.B., N.M., H.O., M.A.H., and J.D.W.G. also contributed to this effort. Notably, T.M.B. assisted us with the crowdsourcing approach, M.A.S. and R.C.C. helped with analyzing speech timing data, and N.M. helped to design the generalized linear models used in this study. J.D.W.G., M.A.H., and H.O. assisted with neuroanatomical classifications.

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