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Direct cortical stimulation of inferior frontal cortex disrupts both speech and music production in highly trained musicians

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ABSTRACT

Music and speech are human-specific behaviours that share numerous properties, including the fine motor skills required to produce them. Given these similarities, previous work has suggested that music and speech may at least partially share neural substrates. To date, much of this work has focused on perception, and has not investigated the neural basis of production, particularly in trained musicians. Here, we report two rare cases of musicians undergoing neurosurgical procedures, where it was possible to directly stimulate the left hemisphere cortex during speech and piano/guitar music production tasks. We found that stimulation to left inferior frontal cortex, including pars opercularis and ventral pre-central gyrus, caused slowing and arrest for both speech and music, and note sequence errors for music. Stimulation to posterior superior temporal cortex only caused production errors during speech. These results demonstrate partially dissociable networks underlying speech and music production, with a shared substrate in frontal regions.

1. Introduction

Music and speech are uniquely human behaviours that are both characterized by complex sequences of motor actions with dynamic acoustic consequences. The extent to which neural representations of speech and music are separate or shared has been a topic of debate for many decades (Koelsch, 2011; LaCroix, Diaz, & Rogalsky, 2015; Patel, 2010; Zatorre, Belin, & Penhune, 2002). Whereas there may be differences in auditory regions like the superior temporal gyrus (STG; Garcea et al., 2017; Katlowitz, Oya, Howard, Greenlee, & Long, 2017), particularly during perception (Norman-Haignere, Kanwisher, & McDermott, 2015; Zatorre et al., 2002), there is increasing evidence for shared representations in prefrontal regions like BA44 (pars opercularis) in the inferior frontal gyrus (IFG; Fadiga, Craighero, & D'Ausilio, 2009; LaCroix et al., 2015; Maess, Koelsch, Gunter, & Friederici, 2001; Özdemir, Norton, & Schlaug, 2006). To date, there have been only limited studies investigating the shared direct roles of left hemisphere core language network regions in music and speech production (Riva, Casarotti, Comi, Pessina, & Bello, 2016), thus it

remains unknown whether areas like left STG, pars opercularis, and ventral sensorimotor cortex (vSMC) are necessary for both behaviours.

To address this question, we used direct electrocortical stimulation (ECS) mapping in two neurosurgical patients who were accomplished musicians. We applied current to the cortical surface of left frontal and temporal regions while these individuals performed a series of speech and music production tasks. Errors evoked by stimulation during the music tasks were compared with those from a standard clinical battery of speech tasks, which included both exogenous stimulus-driven (e.g., repetition, picture naming, auditory naming) and endogenous internally generated (e.g., numerical counting) behaviours. We were specifically interested in comparing both core language functions and more automatic sequential behaviours to the internally generated production of highly familiar music. By examining the specific patterns of errors induced by stimulation to these regions, we demonstrate in these two rare cases that whereas left pars opercularis and vSMC are critical for producing spoken and musical sequences

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(regardless of whether the articulators are the vocal tract or the hands), left STG is critical only for speaking.

2. Method

2.1. Participants

Patient 1 was a 16-year-old, right-handed male with medically refractory epilepsy. He had experienced seizures since age 4, and treatment with anti-epileptic drugs was unsuccessful in managing the frequency and severity of the seizures. Thus, he was a candidate for intracranial monitoring in the paediatric epilepsy unit. During the monitoring period, he participated in ECS mapping procedures, done at the bedside.

Patient 2 was a right-handed male with a left insular low-grade astrocytoma with new onset seizures. At age 25, he underwent surgery to resect the tumour; 23 months later, he underwent a second surgery to resect the regrowth of the tumour. During both intraoperative cases, he participated in awake cortical language mapping, and also played guitar to identify sites that disrupted his ability to perform music.

The study was approved by the University of California, San Francisco (UCSF) Committee for Human Resource Protection Program. Cortical stimulation was conducted for clinical purposes. The participants (and legal guardians in the case of Patient 1) gave written informed consent to participate in the experiments prior to surgery.

2.2. Procedure

Patient 1 was an accomplished classical musician, and in addition to undergoing standard language mapping procedures, he requested prior to surgery that his musical abilities would be preserved. We worked with him in the months leading up to his surgery to custom design a testing protocol that could be used to ensure that resection of the seizure focus did not impair either his language or his musical abilities. Patient 1 specifically learned a piano piece before surgery so that he could perform it during clinical stimulation mapping and electrocorticographic (ECoG) recording (see Martin et al., 2017, for a report on ECoG activity during music production).

To identify the cortical localization of speech and music, we asked Patient 1 to perform five tasks while stimulation was delivered to adjacent bipolar electrode pairs from the implanted electrode arrays. We used four standard clinical stimulation tasks to identify cortical sites that are critical for language: (a) *repetition*, where the participant heard a set of four-syllable words (e.g., "microscopic") and was asked to repeat them aloud (similar procedures are described in Leonard, Cai, Babiak, Ren, & Chang, 2016); (b) *picture naming*, where the participant viewed line drawings of objects and was asked to name the images aloud; (c) *auditory naming*, where the participant heard a description of an object (e.g., "a small flying bug that leaves an itchy bite") and was asked to name the object (e.g., "mosquito"); and (d) *counting*, where the participant was asked to count slowly in increasing order from one to 30, or until instructed to stop.

Patient 1 also performed a task where a full-size electronic keyboard was mounted above the hospital bed. He played the Prelude No. 1 in C Major from the Well-Tempered Clavier Book I by Johann Sebastian Bach several times, as well as standard major scales. Several other piano works were performed through the experiment; however, only the Bach Prelude and scales were used for analysis as he was highly familiar with them prior to his admission, and was able to play them effortlessly. He was instructed to play the piece all the way through once, attempting to continue despite any stimulation-induced errors.

During all five tasks, current was delivered to pairs of electrodes on the implanted ECoG grid. Before the experiments, the clinicians determined which sites on the ECoG grid they would stimulate during each task, targeting motor and auditory regions. Each site was tested between 1 and 18 times ($M = 2.48$, $Mdn = 2.0$, $SD = 2.56$) until at least one of three criteria was met: (a) The patient produced an error that was synchronous with stimulation, (b) after-discharges were observed on the ECoG recordings, indicating that stimulation affected neural activity at the site, or (c) a maximum current amplitude of 6 mA was reached, and neither behavioural errors nor after-discharges were observed.

Patient 2 was an accomplished guitarist, and, like Patient 1, he requested that the resection not interfere with his musical abilities. During an awake craniotomy surgery, an Ojemann bipolar cortical stimulator (Integra LifeSciences, Plainsboro, NJ) with typical settings for mapping (60 Hz, bipolar, biphasic, 1-ms pulse width) was used to perform intraoperative ECS

at a variety of sites in sensorimotor and pre-frontal cortex (Breshears, Molinaro, & Chang, 2015; Chang et al., 2017). He performed the same four standard clinical language mapping procedures, and additionally strummed chords on a guitar. For the purposes of this report, only the counting task was studied in detail, as these data overlapped with regions stimulated during the music task.

2.3. Error analysis

For each task, stimulation-induced errors were identified and characterized according to three phonological categories (substitution, deletion, addition) and two motor categories (slowing, arrest). These error types are described in Table 1, and are based on previously published methods (Leonard, Cai, et al., 2016).

Video files from both the speech and music tasks were extracted from the clinical ECoG monitoring system, and every trial was hand-annotated and transcribed by two of the authors (D.H. and M.D.) using ELAN (ELAN, 2017). Both annotators viewed each video from Patient 1's clinical mapping and annotated instances in which errors occurred. Both annotators were initially blinded to when stimulation occurred. Next, the precise timing of stimulation was determined from the recorded ECoG signals, which showed clear stimulation artefacts. The two annotators independently reviewed the videos, and the separate results were then considered. When there was a disagreement between the two annotators for a particular error, a third annotator evaluated the video, the disagreement was discussed to resolve any discrepancies, and only errors on which there was agreement were included in the final analyses.

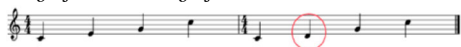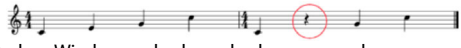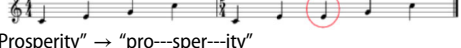Error types were identified on a per-syllable basis for speech tasks and on a per-note basis for the music task. Error categories for the music task were analogous to those for the speech task as in the following examples (Table 1): (a) *Substitutions* were marked if an "E" was replaced by a "D"; (b) *deletions* were marked if a particular note of a sequence was omitted ("C–E–G– →"C–G–); (c) *additions* were marked if a note was inserted within a sequence ("C–E–G– →"C–E–E–G–); (d) *slowing* errors were identified when the tempo of a particular passage slowed down during stimulation and then regained its original tempo after the end of the stimulation train; and (e) *arrest* errors were marked when the participant stopped midway through a musical sequence or was unable to continue playing the sequence. For both speech and music tasks, only errors that occurred within 5 s of stimulation onset were used for the analysis (each stimulation event lasted 3 s).

For each site, task, and error type, the total number of errors and total number of stimulations were counted, and percentage error rates were plotted on a 3D magnetic resonance imaging (MRI) reconstruction of the patient's brain. The electrode locations were determined from a post-operative computed tomography (CT) scan, which was co-registered to the patient's preoperative structural MRI (Hamilton, Chang, Lee, & Chang, 2017). Electrode locations were manually checked and verified to ensure accurate locations and anatomical labelling. For plotting purposes, the stimulation site was marked as the Euclidean mid-point between the two electrodes in each bipolar pair.

2.4. Statistical analysis

To evaluate error patterns statistically, we compared the observed errors to a shuffled distribution. Within each task, error rates were randomly shuffled across sites 1,000 times to generate a null distribution. We

Table 1. Error categories, coding criteria, and examples.

Error category	Error sub-type	Criteria	Examples
Phonological	Substitution	Correct number of phonemes/notes, but production of an incorrect phoneme/note	ntərdʒɛkʃən/ → ɛntərdʒɛkʃən
	Deletion	Missing phoneme/note	dɛləkəsi/ → /ɛləkəsi
	Addition	Extra phoneme/note	Broken Window → brok um brokɛn . . . wɪndəʊ
Motor	Slowing	Phonologically/musically correct, but produced at a slower pace	"Prosperity" → "pro---sper---ity"
	Arrest	Complete halting of production	[no production during stimulation]

then computed 95% confidence intervals for these distributions and compared the observed error rates to determine whether the errors at each site were above the upper bound of the 95% confidence interval for each site.

3. Results

Sites throughout peri-Sylvian cortex were tested during four speech tasks for Patient 1: repetition, picture naming, auditory naming, and counting. Stimulation during each speech task resulted in spatially separable error types. First, we examined which sites were associated with five distinct error types for each speech task (Table 1). The results are summarized in Table 2 and Figures 1 and 2. All reported results were statistically robust, with error rates at each site in each task falling outside the 95% confidence interval of the randomly shuffled null distributions (see Method).

During repetition (16 sites tested), we observed two types of phonological errors (deletion and addition; Figure 1). These errors were associated with stimulation to posterior STG, and involved the same site over the dorsal portion of the gyrus. Speech arrest was also observed at two sites that were clustered in the posterior STG, and included the same site as the one that induced phonological errors (Figure 2).

During picture naming (13 sites tested), we observed one phonological error (substitution), which was induced by stimulation to a posterior STG site that was 4 mm anterior to the sites that showed phonological errors during repetition (the same sites were stimulated in both tasks, but produced errors in only one task; Figure 1). Motor errors were observed with stimulation to posterior STG and inferior temporal gyrus (ITG). Slowing errors were observed when three sites on posterior STG and one site on ITG were stimulated, including the site that caused phonological errors during repetition. Finally, two of the same posterior STG sites as those that caused slowing errors during picture naming also caused speech arrest on other trials. One of these sites (the most posterior-dorsal site) overlapped with a speech arrest site during repetition (Figure 2).

During auditory naming (4 sites tested), we observed a substitution error that was associated with stimulation to one site in the dorsal mid-STG (Figure 1). We also observed speech arrest during stimulation at one posterior STG site that was near sites that caused arrest during repetition (one electrode in the pair was shared across tasks; Figure 2).

Table 2. Summary of stimulation across anatomical regions in Patient 1.

	Temporal			Frontal			Parietal
	STG	MTG	ITG	IFG	Pre-central	Post-central	SMG
Substitution	n = 2	n = 0	n = 0	n = 2	n = 1	n = 0	n = 0
	3.4%	–	–	15.4%	2.9%	–	–
	(M: 0)			(M: 2)	(M: 1)		
	(S: 2)			(S: 0)	(S: 0)		
Deletion	n = 1	n = 0	n = 0	n = 0	n = 1	n = 0	n = 0
	1.7%	–	–	–	2.9%	–	–
	(M: 0)				(M: 1)		
	(S: 1)				(S: 0)		
Addition	n = 1	n = 0	n = 0	n = 0	n = 3	n = 0	n = 0
	1.7%	–	–	–	8.6%	–	–
	(M: 0)				(M: 3)		
	(S: 1)				(S: 0)		
Slowing	n = 4	n = 0	n = 1	n = 3	n = 10	n = 0	n = 0
	6.8%	–	100%	23.1%	28.6%	–	–
	(M: 0)		(M: 0)	(M: 1)	(M: 8)		
	(S: 4)		(S: 1)	(S: 2)	(S: 2)		
Arrest	n = 5	n = 0	n = 0	n = 0	n = 7	n = 0	n = 0
	8.5%	–	–	–	20.0%	–	–
	(M: 0)				(M: 3)		
	(S: 5)				(S: 4)		
Total errors	13	0	1	5	22	0	0
	(M: 0)	(M: 0)	(M: 0)	(M: 3)	(M: 16)		
	(S: 13)	(S: 0)	(S: 1)	(S: 2)	(S: 6)		
Total trials	59	16	1	13	35	7	4

Note: Data are collapsed across tasks, and regions were defined by the Freesurfer anatomical atlas. "M" refers to errors on the music task, and "S" refers to errors on the speech tasks. STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; IFG = inferior frontal gyrus; SMG = supramarginal gyrus.
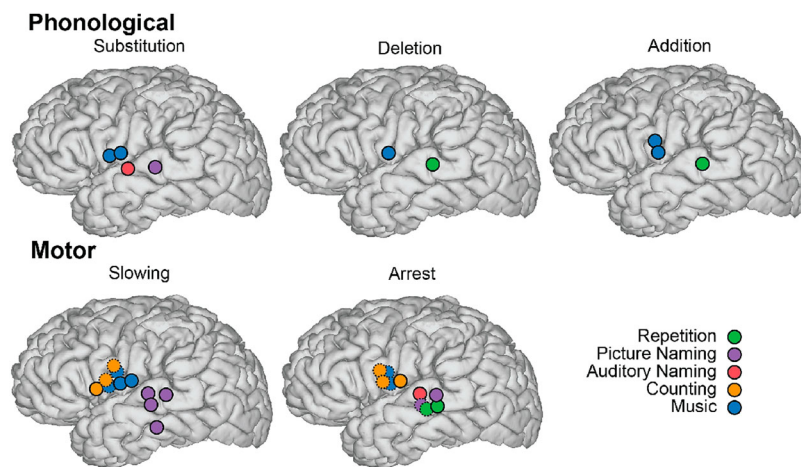
Figure 1. Stimulation-induced errors for speech and music tasks in Patient 1. Error types were divided into phonological (top row) and motor (bottom row), and different patterns of errors were observed across the five different tasks. Sites marked with dotted circles indicate overlap between tasks (markers were shifted for visibility). All sites shown had error rates that were above the 95% confidence interval of a shuffled distribution across all tested sites. [To view this figure in colour, please see the online version of this Journal.]
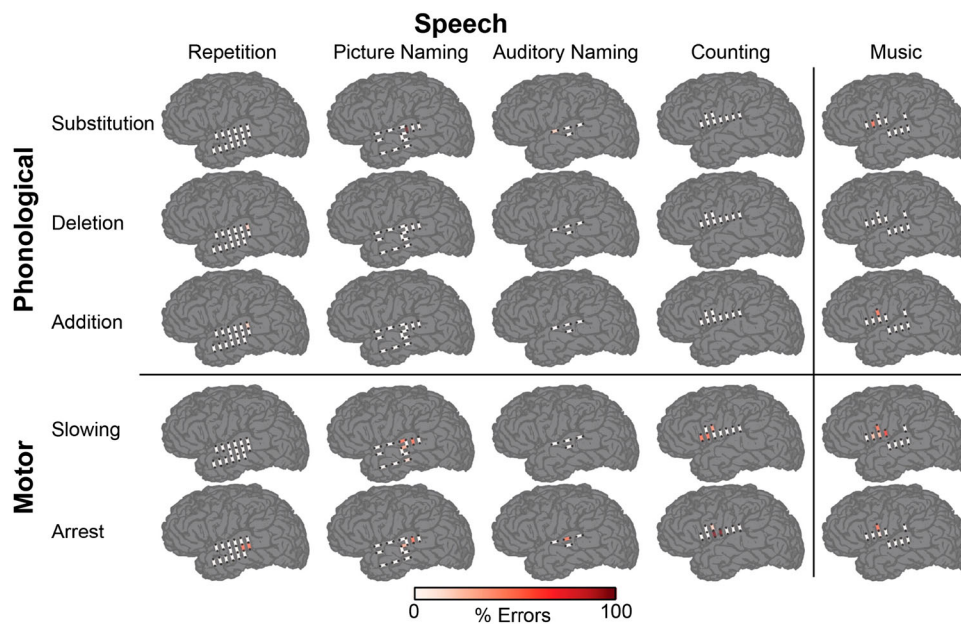
Figure 2. Percentage errors across all error types and tasks for Patient 1. Only electrode pairs that were stimulated for a particular task are shown in each column. [To view this figure in colour, please see the online version of this Journal.]

Finally, during counting (9 sites tested), only supra-Sylvian sites were tested. We did not observe any phonological errors; however, we found multiple sites that caused slowing and speech arrest. Stimulation to posterior inferior frontal gyrus (IFG), and more specifically the pars opercularis, caused slowing and speech arrest, as did stimulation to ventral pre-central gyrus.

We performed a parallel experiment to the speech tasks, where we stimulated a range of temporal and supra-Sylvian cortical sites while Patient 1 played the piano (10 sites tested; all music sites were tested in at least one of the speech tasks). We observed all three types of phonological errors, and both motor errors; however, more instances of motor errors were observed during the task. One site over ventral pre-central gyrus caused substitutions, deletions, and additions (Figure 1 and Figure 2). There was also another site 4 mm dorsal to the pre-central gyrus that caused addition errors, and a site on pars opercularis that caused substitution errors. The same ventral
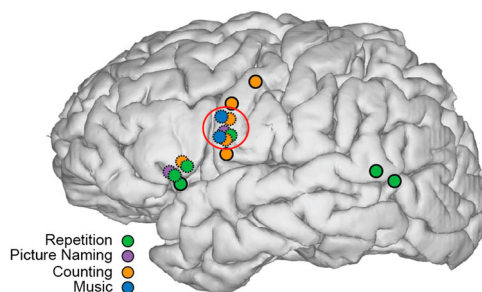
Table 3. Error latencies for Patient 1.

| | Speech | | | | |
	Repetition	Picture naming	Auditory naming	Counting	Music
Substitution	–	0.444 (n/a)	2.856 (n/a)	–	3.727 (n/a)
	$n = 0$	$n = 1$	$n = 1$	$n = 0$	$n = 2$
Deletion	2.013 (n/a)	–	–	–	1.182 (n/a)
	$n = 1$	$n = 0$	$n = 0$	$n = 0$	$n = 1$
Addition	2.404 (n/a)	–	–	–	4.005 (n/a)
	$n = 1$	$n = 0$	$n = 0$	$n = 0$	$n = 2$
Slowing	2.935 (n/a)	0.859 (1.219)	–	**2.959 (1.089)**	**1.166 (0.552)**
	$n = 1$	$n = 4$	$n = 0$	**$n = 4$**	**$n = 9$**
Arrest	3.015 (n/a)	0.435 (n/a)	0.392 (n/a)	**1.846 (1.477)**	**1.678 (0.821)**
	$n = 2$	$n = 2$	$n = 1$	**$n = 4$**	**$n = 3$**

Note: Average (± standard deviation, where applicable) latencies between stimulation onset and error onset for each error type. Bold values indicate a significant difference in stimulation-error latency between counting and music.

Figure 3. Stimulation-induced errors for speech and music tasks in Patient 2. Errors were identified in the three speech tasks (repetition, picture naming, and counting) and for guitar playing (music). Sites marked with dotted circles indicate overlap between tasks (markers have been shifted for visibility). The red circle marks the locations of the two sites that showed stimulation-induced errors during the music task, also overlapping with speech errors. [To view this figure in colour, please see the online version of this Journal.]

pre-central and pars opercularis sites were also associated with both types of motor errors. These sites also overlapped with slowing and arrest errors evoked in the same sites during counting (Figure 1).

We also examined whether there were differences between speech and music in terms of the latency between stimulation onset and error onset. Across all tasks, the average stimulation-error latencies for music and speech tasks were 1.883 and 1.994 s, respectively, $t(32) = 0.243$, $p = .81$ (two-tailed t test with unequal variance). Given the limited number of errors for each task, we only further analysed music versus counting (both endogenously generated behaviours) for slowing and arrest (Table 3). For the purpose of this analysis, we treated arrest errors like "offset" errors, in which behaviour was arrested until after the offset of stimulation. We found a marginally significant effect where slowing errors occurred earlier in music than in counting ($p = .0599$, Mann–Whitney U test). We also examined whether there was a difference in stimulation-error latencies for arrest, and found a marginally significant effect ($p = .0571$, Mann–Whitney U test).

Finally, Patient 2 underwent a similar mapping procedure during an awake surgery, where numerous sites throughout lateral frontal and parietal cortex were tested (Figure 3). During the counting task, we identified sites on ventral pre-central gyrus (anterior bank) that were associated with speech errors. There were two sites in particular where speech arrest was observed on 100% of trials during the first surgery.

The same sites were stimulated while the patient strummed chords on a guitar, and we observed music arrest (i.e., complete immobility of the hands on the strings of the guitar) on 100% of trials (Figure 3). Similar to Patient 1, stimulation at these same sites during rest did not evoke any movement or sensation. During Patient 2's second surgery, the more ventral site was observed to cause both counting and music arrest; however, the exact number of trials for speech arrest during the counting task was not documented. Of note, across both surgeries, these were the only sites that were identified where speech and music arrest occurred, despite testing across lateral frontal and parietal sites (speech-specific errors were observed for repetition, picture naming, and counting in other regions; Figure 3). These results confirm, in an independent replication, the finding that stimulation of ventral pre-central gyrus results in both speech (vocal tract) and music (manual) errors.

4. Discussion

Here, we present two neurosurgical patients whose expert musical abilities allowed us to examine the extent to which the same cortical regions are necessary for speech and music production. We found that similar tasks involving highly practised speech (counting) and musical sequences require left posterior IFG and ventral pre-central gyrus. In contrast, whereas many single word speech production tasks require

posterior STG auditory areas, stimulating those areas during music production does not disrupt behaviour. These dissociations provide novel evidence for partially overlapping cortical networks involved in speech and music.

We found that posterior IFG (pars opercularis) is necessary for both speech (in particular, counting) and music production. In neurosurgery, this region is traditionally thought to be the localized site of Broca's area (Broca, 1861; Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007), as critical surgical decisions are often made to protect this site to prevent Broca's aphasia (Quiñones-Hinojosa, Ojemann, Sanai, Dillon, & Berger, 2003). Although this region is typically thought of as being involved in speech and language, recent evidence suggests that posterior IFG is not specific to speech, but may encode information about movement plans (Swann et al., 2009) and sequencing (Fadiga et al., 2009) in a domain-general manner. Despite its established role in speech, recent work has demonstrated that activity in Broca's area is correlated with linguistic and non-linguistic tasks (Koechlin & Jubault, 2006; Zatorre, Chen, & Penhune, 2007) including music (Koelsch et al., 2002; LaCroix et al., 2015; Maess et al., 2001), and even seems to serve similar functions in non-human primates (Wilson et al., 2015, 2017).

It is particularly striking that we observed disruption in music production for both piano and guitar, which involve different kinds of movements of the hands and arms, further suggesting a more domain-general mechanism. Furthermore, the fact that similar results were observed in a task (counting) that requires the control and movement of the vocal tract, but arguably does not involve the same core linguistic computations as other speech tasks, also suggests a non-linguistic function of this region. These findings of multiple functions attributed to left IFG may in fact reflect a more distributed mode of processing, in which this region plays dynamic and task-dependent roles in concert with other areas that perform parallel computations (Duffau, 2017).

The present results add important information to this emerging picture. In particular, the fact that stimulation to inferior frontal regions causes arrest for both speech and music is consistent with their role in movement planning and execution independent of the specific articulators used (Corina et al., 1999). Furthermore, these regions may be task dependent, and

involve the computation of abstract hierarchical structures necessary to carry out (and possibly understand, Leonard, Baud, Sjerps, & Chang, 2016) complex sequential behaviours (Fadiga et al., 2009; Flinker et al., 2015; Pallier, Devauchelle, & Dehaene, 2011; Rao et al., 2017). The fact that we find both arrest and paraphasic errors in this region, depending on the task, supports the notion that both IFG and ventral pre-central gyrus have multiple functions at both the motor and cognitive levels.

The observation that stimulating the same sites in ventral pre-central gyrus disrupts speech and music production presents a striking and somewhat counter-intuitive result. This region is typically associated with the laryngeal and vocal tract representations of the motor homunculus (Bouchard, Mesgarani, Johnson, & Chang, 2013; Penfield & Jasper, 1954). Here, we showed that stimulating this region disrupts both vocal tract and manual articulator movements. This raises the possibility that ventral pre-central regions are closely linked to neighbouring pars opercularis, and may involve more complex representations that are independent of the articulators (Tate, Herbet, Moritz-Gasser, Tate, & Duffau, 2014).

Finally, a recent case report demonstrated that stimulating right STG caused errors in musical repetition for short phrases, but not for speech (Garcea et al., 2017). This raises the possibility that there is a complex relationship between task complexity (sequences vs. single words or short phrases), hemisphere (left vs. right), and modality (speech vs. music; LaCroix et al., 2015; Tate et al., 2014). The present results complement previous findings by demonstrating that whereas there may be speech-specific representations in left superior temporal cortex (Leonard, Cai, et al., 2016), and music-specific representations in right superior temporal cortex (Garcea et al., 2017), inferior frontal cortex is necessary for both speech and music, perhaps especially when the task involves complex sequences.

There are several aspects of the present study that limit our ability to provide such interpretations unambiguously. First, since both patients were evaluated in neurosurgical contexts for pathological conditions, it is not possible to state whether the results will generalize to healthy populations (although they agree broadly with previous non-invasive neuroimaging and electrophysiological studies). Second, although we observed similarities between the two participants

in the present study, their highly different pathologies (epilepsy and tumour) limit a direct comparison. In particular, since Patient 1 had a chronic condition since childhood, it is possible that cortical reorganization had occurred. Furthermore, differences between bedside mapping (Patient 1) and intraoperative mapping (Patient 2) require different priorities due to time and safety constraints. Thus, although we observed broad agreement between the two patients in the present study, we are unable to fully account for the potential impacts of these differences. Further studies with these types of rare cases will help confirm the results presented here.

Disclosure statement

Funding

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