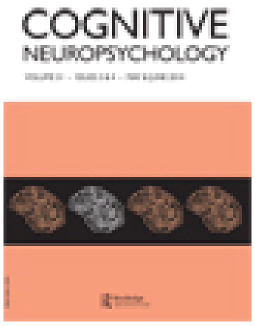

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Direct electrical stimulation of the left frontal aslant tract disrupts sentence planning without affecting articulation

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ABSTRACT

Sentence production involves mapping from deep structures that specify meaning and thematic roles to surface structures that specify the order and sequencing of production ready elements. We propose that the frontal aslant tract is a key pathway for sequencing complex actions with deep hierarchical structure. In the domain of language, and primarily with respect to the left FAT, we refer to this as the 'Syntagmatic Constraints On Positional Elements' (SCOPE) hypothesis. One prediction made by the SCOPE hypothesis is that disruption of the frontal aslant tract should disrupt sentence production at grammatical phrase boundaries, with no disruption of articulatory processes. We test this prediction in a patient undergoing direct electrical stimulation mapping of the frontal aslant tract during an awake craniotomy to remove a left frontal brain tumor. We found that stimulation of the left FAT prolonged inter-word durations at the start of grammatical phrases, while inter-word durations internal to noun phrases were unaffected, and there was no effect on intra-word articulatory duration. These results provide initial support for the SCOPE hypothesis, and motivate novel directions for future research to explore the functions of this recently discovered component of the language system.

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Introduction

Sentence production requires planning at multiple levels of processing. Planning is needed to grammatically structure phrases, position lexical elements and grammatical morphemes, and retrieve and ultimately produce phonological and articulatory information. Understanding the neural circuitry that supports sentence production is critical for understanding how the brain processes language. Strong constraints on cognitive models are provided by careful studies of how the system can fail, either in the healthy system in the form of slips of the tongue or under conditions of neurological injury. The Frontal Aslant Tract is a recently discovered white matter pathway that connects, in one branch, the inferior frontal gyrus to the pre-supplementary motor area, and in another branch, the inferior frontal gyrus with the anterior cingulate cortex. Within the inferior frontal gyrus it is believed to project principally to pars opercularis, but there is also evidence that it may project to pars orbitalis (Szmuda et al., 2017). The anatomy of the Frontal Aslant Tract was formalized in human Diffusion Tensor Imaging (DTI) tractography studies by Catani et al. (2012, 2013) and previously described by others (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Ford, McGregor, Case, Crosson, & White, 2010; Lawes et al., 2008). Post-mortem dissection of human brains (Bozkurt et al., 2016; Goryainov et al., 2017; Koutsarnakis et al., 2017) and tractography studies in nonhuman primates (Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012) have also provided important information about the anatomy of the frontal aslant tract.

Lesions to the left frontal aslant tract can result in halting and dysfluent speech that is otherwise semantically, morpho-syntactically, and phonologically correct; furthermore, the dysfluency in spontaneous sentence production does not manifest during sentence repetition (Chernoff et al., 2018). A broader literature has implicated the FAT in verbal fluency, in primary progressive aphasia (Catani et al., 2013; Mandelli et al., 2014), autism (Chenausky, Kernbach, Norton, & Schlaug, 2017), and post-stroke language difficulties (Li et al., 2017). There is also evidence for a role of the FAT in speech initiation. Direct electrical stimulation

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intra-operatively of left frontal aslant tract has been shown to be able to induce speech arrest (Vassal, Boutet, Lemaire, & Nuti, 2014). Further, when examining post-operative outcome after damage to the frontal aslant tract as compared to the fronto-striatal tract (which is located more medially), damage to the former was more likely to cause speech initiation impairments, while damage to the fronto-striatal tract caused non-speech motor initiation impairments (Fujii et al., 2015; Kinoshita et al., 2014). Damage to the frontal aslant tract has also been related to a reduction in functional connectivity between its cortical endpoints (Chernoff et al., 2018), suggesting that functional connectivity of those structures critically depends on the FAT and not other pathways.

The frontal aslant tract, in addition to the corticospinal and corticobulbar (Cai et al., 2014; Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Dick, Bernal, & Tremblay, 2014) has been associated with stuttering, both developmentally (Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2016a, 2016b) and intra-operatively (Kemerdere et al., 2016). While the right frontal aslant tract has not been as systematically studied, Dick, Garic, Graziano, and Tremblay (2018) have suggested that the right FAT may play a critical role in executive function, especially inhibitory control. That proposal resonates with the putative role of the right inferior frontal gyrus in inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Verbruggen & Logan, 2008), and the pre-supplementary motor area in selection of movements (Amador & Fried, 2004) and resolving conflicting motor plans (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007).

Here we propose that the left frontal aslant tract serves as an interface between distinct levels of sentence planning—specifically, between planning syntagmatic relations and positional planning of morphophonological elements—we refer to this as the "Syntagmatic Constraints On Positional Elements" (SCOPE) hypothesis. The key aspect of this proposal is that the frontal aslant tract interfaces grammatical specifications of sentence structure with (already accessed) lexical representations, by hypothesis, in anticipation of planning articulatory phrases. This generates the prediction that disruption of the frontal aslant tract should specifically disrupt sentence production at phrasal boundaries, with no impairment for articulatory duration. The purpose of the current investigation was to test that hypothesis by measuring sentence fluency, in a patient who was anticipated to have direct electrical stimulation of the left frontal aslant tract during surgery for resection of a tumour.

Prior documented impairments for speech fluency in patients with damage to the FAT have been based on neuropsychological tests of speech production—such as the BDAE "Cookie Theft" (Chernoff et al., 2018) test, the "Cinderella test" (Catani et al., 2013), and indices of stuttering severity, such as the Stuttering Severity Instrument (SSI-III; Riley, 1994). While powerful, those tests capture gross fluency measures (such as mean length of utterance), and are less constrained than may be preferable for evaluating our proposal about the functions supported by the frontal aslant tract. We thus designed a task that could be used intra-operatively while the frontal aslant tract was stimulated, and which would allow us to examine different components of sentence production. The patient was presented with a 2×2 arrangement of coloured geometric shapes on each trial, with one of the four shapes cued via a thick black outline. The patient's task was to generate a sentence describing the spatial relation of the cued shape in relation to the shape that was either immediately above or below it—for instance, "The red square is above the yellow circle". If stimulation of the frontal aslant tract disrupts sentence production by disrupting lexical retrieval, then we predict that inter-word durations (i.e., pauses between words) will be longer prior to all content words in the sentence. By contrast, if the frontal aslant tract supports integration of grammatical information with positionally specified elements, then stimulation of that tract should lead to prolonged inter-word durations at the boundaries of grammatical phrases, but not within grammatical phrases. Finally, if the frontal aslant tract supports articulatory processes, then stimulation of that tract should prolong or disrupt articulation of all words in the sentence.

Methods

Participants

Patient AI was, at the time of testing, a 46 year-old man with a left frontal Oligodendroglioma (Figure

1A) who was recruited as part of an ongoing prospective longitudinal study evaluating preoperative fMRI and DTI for delineating the maximal safe surgical resection. Eleven age matched neurosurgical controls completed the same neuropsychological tests (see Garcea et al., 2017 for precedent with those controls). All patients gave informed consent in compliance with procedures set by the institutional review board of the University of Rochester.

MRI data acquisition parameters

A series of BOLD fMRI, T1 and DTI studies were conducted with AI to localize language, sensorimotor, and praxis networks as part of pre-surgical planning. Those scans constitute a standard regimen of scans conducted on all neurosurgery patients studied within the Program for Translational Brain Mapping at the University of Rochester (www.tbm.urmc.edu).

MRI data were acquired on a 3 T Siemens PRISMA scanner with a 32-channel head coil located at the Rochester Center for Brain Imaging. High-resolution structural T1 contrast images were acquired using a magnetization prepared rapid gradient echo (MPRAGE) pulse sequence at the start of each session (TR = 2530, TE = 3.44 ms, flip angle = 71, FOV = 256×256 mm^2, matrix = 256×256, voxel size $1 \times 1 \times 1$ mm^3, 192 sagittal slices). Functional images were acquired using a BOLD echo-planar imaging pulse sequence (TR = 2200 ms, TE = 30 ms, flip angle = 70, FOV = 256×256 mm^2, matrix = 128×128, voxel size = $2 \times 2 \times 2$ mm^3, 90 axial slices). DTI acquisition used a single shot echo-planar sequence (60 diffusion directions with b = 1000 s/mm^2, 10 images with b = 0 s/mm^2, TR = 6500 ms, TE = 56 ms, FOV = 256×256 mm^2, matrix = 128×128, voxel size = $2 \times 2 \times 2$ mm^3, 70 axial slices, anterior to posterior phase encoding). One additional b = 0 volume was collected with posterior to anterior phase encoding, to allow for susceptibility induced artifact correction.

fMRI preprocessing

fMRI data were analyzed with the BrainVoyager software package (Version 2.8) and in-house scripts drawing on the BVQX toolbox written in MATLAB. The first six volumes of each run were discarded to allow for signal equilibration (four at image acquisition and two at preprocessing). Preprocessing of the functional data consisted of (in order) slice scan time correction (sinc interpolation), motion correction with respect to the first volume of the first functional run, and linear trend removal in the temporal domain (cutoff: Two cycles within the run). Functional data were registered (after contrast inversion of the first volume) to high-resolution de-skulled anatomy of each subject in native space. Functional data were smoothed at 6 mm FWHM (1.5 mm voxels), and interpolated to 2 mm^3 voxels. These analysis pipelines are described in prior work from our group (e.g., Chen, Garcea, & Mahon, 2016, 2017; Chernoff et al., 2018; Fintzi & Mahon, 2013; Garcea, Kristensen, Almeida, & Mahon, 2016; Garcea et al., 2017; Garcea & Mahon, 2014; Kristensen, Garcea, Mahon, & Almeida, 2016; Mahon, Kumar, & Almeida, 2013).

Diffusion MRI preprocessing

DTI preprocessing was performed with the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). Susceptibility induced artifacts were corrected using FSL's TOPUP tool (Andersson, Skare, & Ashburner, 2003; Smith et al., 2004). Next, the coefficients from TOPUP were fed to FSL's Eddy tool (Andersson & Sotiropoulos, 2016), which corrects eddy currents and motion. Lastly, reconstruction of the whole brain tensor was performed using StarTrack (https://www.mr-startrack.com/) with a step size of 1 mm, angle threshold of 45 degrees, and FA threshold of 0.2.

Definition of functional ROIs for tractography

One of the language scans—a category fluency experiment—was used to functionally localize regions of interest (ROI) to perform tractography. In the category fluency experiment, the patient viewed a cue that could be a letter (e.g., words that start with the letter "a"), a noun (e.g., fruit), or an action category (e.g., actions performed in the kitchen), and had 30 s to overtly generate as many items from that category as possible. Stimulus blocks alternated with 20-second fixation periods. Regions of interest (ROI) for tractography were functionally defined using the peak BOLD-contrast from the category verbal fluency tasks, in the pre-supplementary motor area and the posterior inferior frontal gyrus. Ten-millimeter radius spheres were drawn around the peak voxel and used as seeds for fiber tracking.

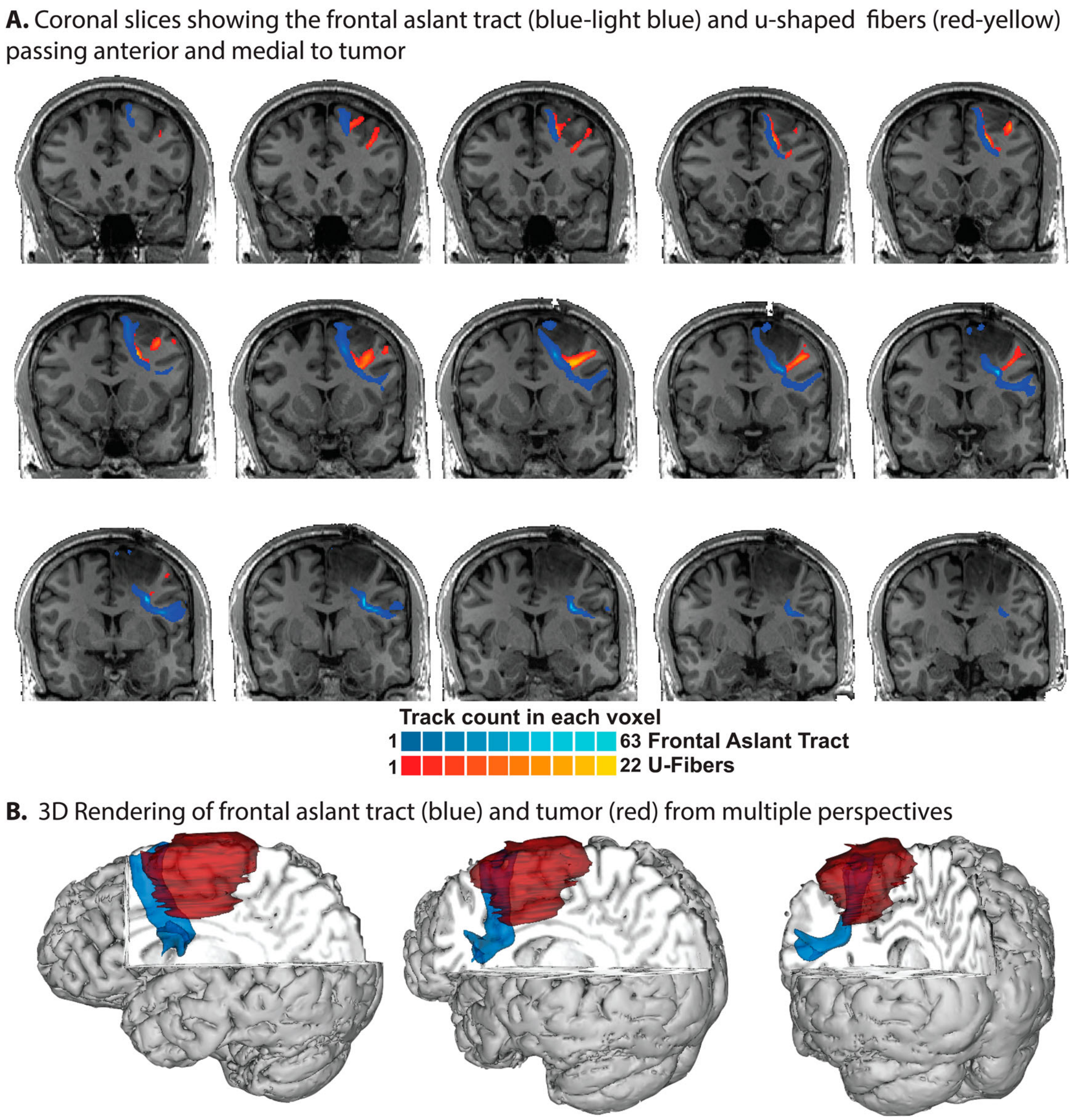

Figure 1. (A) Coronal series showing the frontal aslant tract (blue-light blue gradient), the u-shaped fibers connecting the middle and superior frontal gyrus (red-yellow gradient), and the lesion visible in the T1 image, with track counts in each voxel. (B) Three dimensional reconstruction of the tumour (red) and the left frontal aslant tract (blue) in the patient's pre-operative T1-weighted MRI. To view this figure in colour, please see the online version of this journal.

An exclusion mask was drawn around consecutive sagittal slices in the right hemisphere, four to eight millimetrs from the midline, in order to exclude crossing callosal fibers. Deterministic tractography was performed using TrackVis (Wang, Benner, Sorensen, & Wedeen, 2007).

Neuropsychological tests

Patient AI was evaluated pre-operatively to broadly assess language, praxis, visual processing, memory, and attention. All testing was video and/or audio recorded for offline analysis (for a detailed descriptions of the testing, see Garcea, Dombovy, & Mahon, 2013; Stasenko, Garcea, Dombovy, & Mahon, 2014). We conduct a large array of tests as part of a standard battery for a broader longitudinal study in the Program for Translational Brain Mapping, but in this case we were particularly interested in language function. The purpose of testing patients more broadly is to understand the limits of each patient's impairments, which is critical for deriving inferences about cognitive organization based on the underling cognitive processes that are disrupted in any given patient (i.e., the "sufficiency" condition, as in Caramazza, 1984).

AI completed a neuropsychological screener prior to surgery and again one month after surgery. Language assessment included picture naming (Snodgrass & Vanderwart, 1980), word reading (Psycholinguistic Assessment of Language Processing in Aphasia, PALPA, subtest 33; Kay, Coltheart, & Lesser, 1992), pseudoword reading (PALPA subtest 36), number reading (one, two, and three digits), category fluency (1 min to generate items to letter, category or action-context cues), sentence repetition (PALPA, subtest 12, subset of $n = 18$), picture-word matching (Stasenko et al., 2014), and object decision (Barbarotto, Laiacona, Macchi, & Capitani, 2002). AI was also evaluated for praxis knowledge using in-house materials and procedures described previously (Garcea & Mahon, 2012, 2013; for precedent, see Buxbaum & Saffran, 2002). AI was unimpaired for all neuropsychological tests preoperatively (see Table 1).

Task for intra-operative direct electrical stimulation mapping

Intra-operative stimulation of the frontal aslant tract has been performed almost exclusively using picture naming and limb movements, with the exception of Sierpowska et al. (2015), who also used a verb-from-noun generation task. In order to assess sentence planning within the constraints of the operating room, we designed a task with simple geometric shapes, and which involved an overt response to facilitate real-time scoring of accuracy in the service of proximate clinical decisions about how to procede with the tumour resection. We also designed the task to be amenable to detailed response time analysis in order to evaluate the core prediction made by the SCOPE hypothesis (see Introduction). To elicit sentences that were standardized and predictable, geometric shapes (square, circle, triangle, and diamond) that were each one of four colours (blue, yellow, red, or green) were arranged in a 2 by 2 array on each trial. On each trial, one of the four shapes had a thick black outline, which indicated it was the target shape, and hence the grammatical subject of the sentence (Figure 3). The patient's task was to describe the spatial relation between the target shape and the shape that was either above or below it, using as much information as is required. For example, when presented with two triangles above two circles, the patient could say "The blue triangle is above the red circle". The task allows for pragmatic constraints to influence syntactic structure (e.g., it would be as informative in that example to say "The triangle is above the red circle" because there is only one red circle). In contrast, for other trials, in which all four items were different shapes, the task could be accurately completed without using colour terms (e.g., "The triangle is above the square"). This manipulation, in principle, introduces variation in the frame of the sentence. Similar approaches using displays of shapes to elicit sentences have been used to test utterance planning and message formulation (e.g., Brown-Schmidt & Tanenhaus, 2006). We note, that in the end, the patient always produced sentences of the form "The [color] [shape] is [above/below] the [color][shape]". Because the patient was otherwise fully on task during the awake portion of the surgery, he was not corrected or encouraged to use the alternate (i.e., more minimal) sentence frames.

There are many permutations of shapes*colour*-position*target so we randomly sampled 100 combinations for materials to be used, with the constraint that there were 25 trials of each of the four possible minimalistically correct sentence frames (i.e., no colour terms, two colour terms, or colour term for first or second shape only). AI practiced the task in

Table 1. Neuropsychological performance of patient AI and 11 age matched neurosurgical controls.

Category	Test	Patient AI Accuracy	Neurosurgical Controls Mean Accuracy	SD
Naming	Word reading	100%	96%	5%
	Pseudoword reading	96%	90%	16%
	Number naming	100%	77%	17%
	Picture naming	95%	94%	5%
Semantic Processing	Object decision	96%	89%	10%
	Picture-word match	100%	97%	3%
Other	Sentence repetition	100%	93%	14%
	Function knowledge	100%	96%	7%
	Manipulation knowledge	100%	83%	25%
	Cambridge face test	80%	71%	16%
Verbal Fluency		Average number of items		
	Letter fluency	18.33	19	2
	Noun fluency	18.50	14.1	4.7
	Action fluency	17.67	11.5	3.62

Note: Values in the table represent percent correct, with the exception of category fluency (mean number of items).

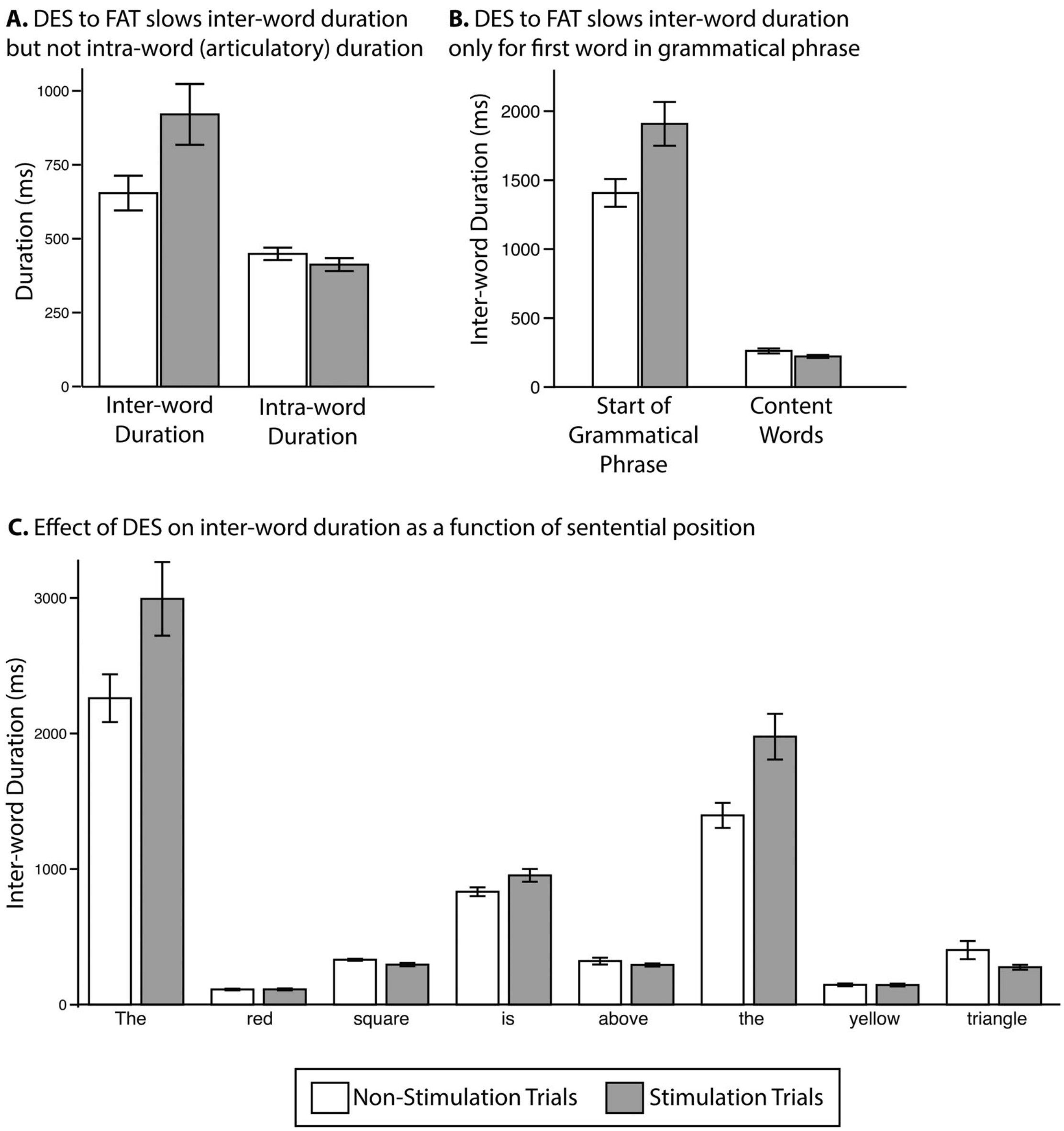

Figure 3. (A) Inter- vs. Intra-word durations**.** Mean inter-word durations for each correct word and mean articulation time for each correct word. Averages are compared for stimulation trials (grey bars) and non-stimulation trials (white bars). Error bars show the standard error of the mean, over words. (B) Phrase head vs. content word inter-word duration; Mean inter-word duration is compared across all phrase head words and across all content words, for each correct word. Averages are compared for stimulation trials (grey bars) and non-stimulation trials (white bars). Error bars show the standard error of the mean, over words. (C) Mean inter-word duration for each ordinal position of the sentence. Averages are compared for stimulation trials (grey bars) and non-stimulation trials (white bars). Error bars show the standard error of the mean, over trials. To view this figure in colour, please see the online version of this journal.

the lab prior to surgery, laying down on his right side, to simulate the ergonomics of the operating room. During those practice sessions, he understood the task and performed all trials with no errors, hesitations, or paraphasias. During the surgery, an auditory cue (a click) initiated each trial; this auditory cue signalled to the surgeon the start of a new trial. At the discretion of the attending surgeon (WHP) direct current stimulation was then applied coincident with trial onset, with the duration of stimulation lasting ~4 s.

Intra-operative testing

Intra-operative experiments were performed using StrongView, which has been developed within the Program for Translational Brain Mapping at the University of Rochester. StrongView includes a PC with a keyboard for experiment control, an independent backup battery power source, and speakers (Bose Companion 2 Series III). An articulating arm (Tether Tools Rock Solid Master Articulating Arm) that can rotate along multiple joints with several degrees of freedom is attached via a rail clamp to the surgical bed. Attached to the arm is a small touch screen (Elo 1002 L 10″ Touchscreen Monitor), a microphone (Sennheiser Professional Shotgun Microphone), and a webcam (Logitech HD Pro Webcam C920), all of which are trained on the patient's mouth. The microphone feeds through a splitter (M-Audio M-Track) that goes to (i) an amplifier (Behringer Tube Ultragain Mic100) and directly to a speaker, so that both the surgeons and the researchers can hear the patient with no delay/echo, and (ii) to the PC where it is timestamped and recorded for offline analysis. In-house software (StrongView) controls presentation and randomization of stimuli, and inter-trial and inter-stimulus intervals. StrongView records the timestamp at which each stimulus is presented, and a photodiode on the patient screen is fed to the electrocorticography amplifier to mark trial onsets (data not analyzed herein). A camcorder (Sony HDR-CX900 HD Handicam) positioned on an 11-foot tripod was used to record the surgery in high definition. In addition, an overhead camera built into the operating lights recorded the entire surgery. Cranial navigation was accomplished with BrainLab, which is an optical camera system that aligns the patient's brain to the preoperative MRI using facial physiognomy. Prior to mapping, a BrainLab registration star was attached to the bipolar direct current electrical stimulator and registered using the fixed registration star on the field. In this way, we acquired the exact location of each point of direct electrical stimulation with respect to the preoperative MRI. Those data points were exported after the case for offline analysis, and are shown as red spheres in Supplemental Video 1.

Response time analysis of the experimental task

Inter-word (i.e., pauses between words) and intra-word (i.e., articulatory) durations were calculated by manually transcribing the audio using Audacity by author BC. At the time of analysis, BC was blinded to which trials were with stimulation and which were without stimulation (he did not attend the mapping session and reviewed video records of the surgical field only after performing the latency analyses). We coded each word with its ordinal position within the sentence (i.e., "is" is position number four; <above/below> is position number five, etc.). In addition, a binary variable was coded for each word that represents whether or not the word was part of a trial where subcortical direct electrical stimulation was applied. The inter-word duration for a given word was defined as the difference between the offset of the last phoneme of the previous word, and the onset of the first phoneme of the current word. The intra-word duration (articulatory duration) of a given word was defined as the difference between the onset of the first phoneme of a word and the offset of the last phoneme of that word. A schematic of the sentence parcellation scheme adopted herein is depicted in Figure 2.

Determining proximity of stimulation points to the frontal aslant tract

In order to calculate Euclidean distance from each stimulation point to the frontal aslant tract, we used FSL to extract the entire set of coordinates ($n = 2580$) that correspond to the FAT, based on pre-operative DTI. FSL's linear registration tool (FLIRT) (Jenkinson & Smith, 2001) was used to register the pre-operative frontal aslant tract to the T1 anatomy used for intra-operative navigation. Separately, and as described above, we used BrainLab for cranial navigation in the operating room to record the coordinate of each location of intraoperative stimulation. For each stimulation coordinate, we calculated the Euclidean distance to each of the 2580 voxels of the frontal aslant tract. The minimum value from the resulting vector was taken as the estimate of the Euclidean distance between the stimulation point and the closest point along the frontal aslant tract.

Results

Intra-operative mapping to identify eloquent cortical sites initiated with motor mapping and picture naming. Direct electrical stimulation was delivered with a bipolar Ojemann stimulator (Nicolet). There were no motor- or language-positive sites in the area of planned corticectomy. On that basis, the surgeon began the tumour resection. From preoperative MRI (fMRI + DTI), we knew that the tumour was

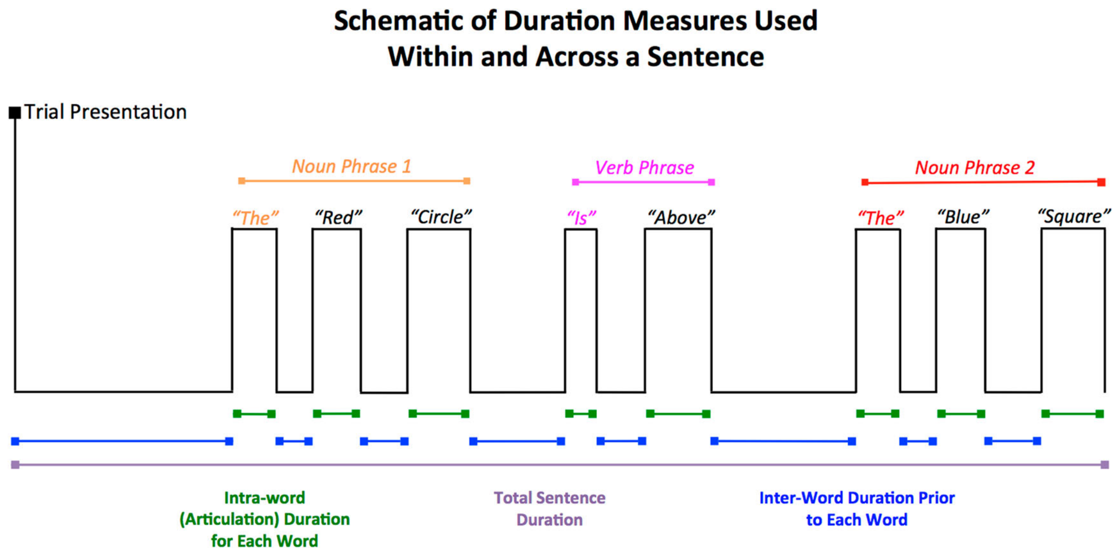

Figure 2. Schematic of the sentence latency measures used in the present investigation- The black square represents the onset of each trial. The words are grouped into noun phrases (orange and red) and the verb phrase (magenta), where the first word of each phrase represents the phrasal boundary. The gaps highlighted in green represent articulatory time (i.e., intra-word durations), while the gaps highlighted in blue represent inter-word durations. The purple gap represents the entire sentence duration. To view this figure in colour, please see the online version of this journal.

located anterior to motor cortex, with the anterior margin of the tumour abutting the posterior aspect of the frontal aslant tract, at the tract's superior/medial end.

After the incision was made and the tumour resection had initiated, AI performed 19 trials of the sentence production experiment without stimulation. This provided a "warm-up" for the patient on the critical task. During this "practice" session, only one error was produced, which was self-corrected (diamond to triangle). He also performed sentence repetition using sentences from subtest 12 of the PALPA (Kay et al., 1992). No repetition errors, paraphasias, or stuttering were observed. Those observations are important because they indicate that the corticectomy itself had no effect on AI's language abilities.

Toward the end of the tumour resection, when the frontal aslant tract was exposed after resection of the anterior margin of tumour, the experimental task was initiated. Thirty-eight trials of the experiment were completed by AI, with 18 of those 38 trials accompanied by subcortical stimulation along the deep anterior margin of the tumour, and 20 without stimulation. For all of those trials, AI produced sentence frames that included colour terms for both shapes (e.g., The COLOR SHAPE is ABOVE/BELOW the COLOR SHAPE). Of the 304 words he produced across the 38 sentences (38 trials * 8 words), 251 were included in the latency analyses. The words excluded from latency analysis included instances of speech arrest or hesitation ($n = 20$), coordinate substitution ($n = 9$), and word productions preceded by non-verbal sounds such as coughing ($n = 9$). After the first pass latency analysis, statistical outliers ($n = 15$) were excluded, defined as words with a preceding inter-word pause that was 2 standard deviations or greater than the mean inter-word pause for all words at that sentence position. There were no phonemic substitutions or articulatory errors. The mean distance of all stimulation points to the FAT was 10.2 millimetrs (SD = 5.4; range 1.14–17.69).

Accuracy

We considered all correct words in the inter-word pause analysis, but we also looked at accuracy at the trial level. While words were excluded if they were preceded by a cough or were outliers, those sentences were considered accurate for sentence-level analyses, in that he eventually produced the correct description of the shapes with no paraphasias. Of the 18 stimulation trials, AI made errors on 9 trials, including coordinate substitutions (orientation, shape, or colour words), and speech arrest. The other 50 of the stimulation trials were correct. Conversely, of the 20 non-stimulation trials, AI made two errors. On one trial he said “below” instead of “above”, and on another trial he failed to complete the full sentence prior to the onset of the next trial. The difference in accuracy between stimulation and non-stimulation trials was significant ($X^2_{38} = 7.37$, $p = 0.007$).

Latency analysis

Total sentence duration was not different for correct stimulation trials compared to non-stimulation trials ($t_{25} = 0.41$, $p = 0.68$). Sentence duration was calculated from the onset of the stimulus to the offset of the last word.

We examined articulation time of stimulation and non-stimulation trials, in order to test whether stimulation affected the time required to produce the speech motor movements of each word. The mean articulation time for words with stimulation was 413 ms (SD = 236 ms; range = 127–885 ms) and for words without stimulation was 449 ms (SD = 257 ms; range = 129–1162 ms); the difference was not significant ($t_{249} = 1.15$, $p = 0.25$, $d = 0.15$) (Figure 3A).

We then examined the effect of stimulation on inter-word durations. We conducted a two-way analysis of variance (ANOVA) to test the influence of stimulation (2 levels: Stimulation, no stimulation) and sentence position (8 levels: First | second | third | fourth | fifth | sixth | seventh | and eighth word in the sentence) on inter-word durations. There were main effects of stimulation ($F_{(1,235)} = 11.15$; $p = 0.001$, $\eta^2_p = 0.05$) and position ($F_{(7,235)} = 191.52$, $p < 0.00001$; $p < 0.02$, $\eta^2_p = 0.85$), and an interaction between stimulation and position ($F_{(7,235)} = 5.92$, $p < 0.00001$, $\eta^2_p =$ 0.15). Hypothesis driven tests evaluated the key question of whether inter-word durations were differentially prolonged at phrasal heads, including for the verb (“is”) and noun phrases (“the”). For this analysis, we binned across sentence positions according to grammatical structure. Specifically, inter-word durations prior to the noun phrases (prior to “the”) and prior to the verb (“is”) were combined, while inter-word durations prior to all other words were combined (Figure 3B). There was a two-way interaction between position and stimulation ($F_{(1,247)} = 13.386$, $p = 0.0003$, $\eta^2_p = 0.05$). This interaction is reflected in the higher mean for “the” and “is” after stimulation (mean = 1908 ms, SD = 1076 ms) compared to without stimulation (mean = 1407 ms, SD = 699 ms), but a *lower* mean for all other words when produced in the context of stimulation (mean = 221 ms, SD = 91 ms) compared to without stimulation (mean = 261 ms, SD = 175 ms).

Finally, we conducted *t*-tests for stimulation vs. non-stimulation for inter-word durations at each position in the sentence (Figure 3C). There were significant differences for words in the first ordinal position (“The”) ($t_{25} = 2.23$, $p = 0.04$, $d = 0.86$); the third ordinal position (shape) ($t_{31} = -2.64$, $p = 0.01$, $d = 0.91$); the fourth ordinal position (“is”) ($t_{34} = 2.14$, $p = 0.04$, $d = 0.71$); and the sixth ordinal position (“the”) ($t_{29} = 3.08$, $p = 0.004$, $d = 1.1$). There were no significant differences in inter-word durations between stimulation and non-stimulation words for the other ordinal positions.

Discussion

The frontal aslant tract is a recently described white matter pathway that connects the inferior frontal gyrus with supplementary motor cortex, and has been implicated in verbal fluency in a series of reports. We propose a new hypothesis for understanding the contribution of the frontal aslant tract to language production, emphasizing the role of this pathway in mapping grammatical specified planning of sentence structure and positional level planning—referred to as the Syntagmatic Constraints On Positional Elements (SCOPE) hypothesis. One prediction made by this proposal is that disruption of the FAT will disrupt sentence production at the level at which syntagmatic relations interface with positional specifications of words, which by hypothesis, should correspond to the boundaries of grammatical phrases. To test this prediction, we designed a cued sentence production task for use during intraoperative awake language mapping, and analyzed both accuracy and the distribution of intra- and inter-word durations as a function of stimulation. We found that neither the overall duration of sentences nor the articulation time (intra-word durations) of words was affected by stimulation. However, inter-word durations were prolonged for words preceded by stimulation of the frontal aslant tract, but only if those words were at the boundaries of grammatical phrases. Other words were either not significantly different, or facilitated by stimulation (shorter inter-word durations for stimulation than non-stimulation). One possibility is that the facilitation observed for inter-word durations within noun phrases is a byproduct of the prolonged durations at the boundary of the noun phrase; i.e., there was more time devoted to planning the entire phrase, and some of that time allowed articulatory planning to proceed as well. To evaluate this possibility, we correlated the inter-word durations for the boundary of the second noun phrase in each sentence with the within-phrase inter-word durations (also for the second noun phrase in each sentence). This was done separately for stimulation and non-stimulation trials. If facilitation effects are a byproduct of more time devoted to planning the phrase at its initiation, then there should be a negative correlation. In contrast, we observed a positive correlation ($r = 0.44$) between inter-word durations for the head of the second noun phrase and inter-word durations within that phrase. Thus, at present, it is not obvious why stimulation would lead to shorter inter-word durations *within* noun phrases, and this issue merits additional empirical scrutiny with future research.

All models of speech production agree that sentence production involves the (i) formulation of a message, (ii) construction of a syntactic frame together with access to words' grammatical properties, and (iii) phonological encoding and articulation (e.g., Caramazza, 1997; Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Garrett, 1980a, 1980b; Rapp & Goldrick, 2000). While models disagree on issues such as the dynamics of information flow in the system, whether there are 1 or 2 lexical levels, and whether access to syntactic and phonological properties occurs in that order or in parallel, there is broad agreement that sentence production involves the translation of a hierarchical representation specifying sentence-level grammatical dependencies into a specific surface form. Furthermore, there is general agreement that grammatical processing is a separable process in language production, and there is substantial neural evidence as well (Friederici, Bahlmann, Heim, Schubotz, & Anwander, 2006; Hickok & Poeppel, 2007; Indefrey & Levelt, 2004; Shapiro, Shelton, & Caramazza, 2000; Shapiro & Caramazza, 2003; Shapiro, Moo, & Caramazza, 2006). Thus, all models must posit a process whereby grammatical specifications are "realized" as surface forms. Our proposal is that the frontal aslant tract is a key component of that interface.

Our findings are relevant as well to previous research on the functional consequences of damage to the cortical regions connected by the Frontal Aslant Tract—the inferior frontal gyrus (IFG) and pre-supplementary motor area (pre-SMA). The IFG is associated with agrammatism in primary progressive aphasia, both in production (Grossman, 2012) and comprehension (Charles et al., 2014). Lesion studies have also implicated the IFG in syntactic processing (Grodzinsky, 2006; Kaan & Swaab, 2002). Importantly, the IFG has been implicated in a number of other aspects of language processing, including phonological encoding, selection among alternatives and general control processes (e.g., Anders, Riès, Van Maanen, & Alario, 2017; Kan, Kable, Van Scoyoc, Chatterjee, & Thompson-Schill, 2006; Nozari & Hepner, 2018; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Thompson-Schill, Bedny, & Goldberg, 2005), and it has been argued that this brain region is composed of functionally distinct subregions (Amunts et al., 1999; Anwander, Tittgemeyer, von Cramon, Friederici, & Knösche, 2006; Heim, Eickhoff, & Amunts, 2008; Sahin, Pinker, Cash, Schomer, & Halgren, 2009). If the IFG is composed of functionally distinct subregions, then it is important to consider if the FAT consists of functionally dissociable tracts with different endpoints in different subregions of the of IFG. Pars opercularis and pars triangularis are the regions of the IFG most commonly described as the endpoints of the FAT (Dick et al., 2018), and an important open question is whether there may be different subcomponents of the FAT, projecting to different regions of the IFG, that support different functions.

At the other end of the FAT, the pre-SMA has been shown to support the organization of action sequences (Kennerley, Sakai, & Rushworth, 2004), especially when it comes to initiation (Eccles, 1982; Nachev et al., 2007 for review). There is some evidence that the *right* hemisphere FAT may support the initiation and control of motor movements generally, as damage to the right FAT can result in Foix-Chavany-Marie syndrome, an impairment of voluntary control of certain facial and pharyngeal movements (e.g., laughing, coughing) with intact reflexes in the same muscles (Brandao, Ferreria, & Leal Loureiro, 2013; Martino, de Lucas, Ibanez-Plagaro, Valle-Folgueral, & Vazquez-Barquero, 2012). These impairments have not been observed after damage to the left FAT, which may support a dissociation between the left and right hemisphere FAT (Dick et al., 2018). It is important to emphasize that while we have framed the SCOPE hypothesis as applying to *sentence* production, there is nothing in our data that precludes a role for the FAT in relating other hierarchically organized action sequences to planning processes necessary for their production. Whether or not the left FAT supports similar functions outside of language as it does, by hypothesis, in language is an important and open empirical question.[1]

There are several limitations of the current investigation that should be considered in interpreting our findings and in thinking forward to future empirical investigations of the FAT. First, other white matter pathways share a common endpoint with the frontal aslant tract in the inferior frontal gyrus, such as the Arcuate Fasciculus (AF). However, it is unlikely those other pathways were directly affected by stimulation because all subcortical stimulations were at the level of the superior frontal gyrus and not the inferior frontal gyrus. It is possible, however, that the effect on behaviour of frontal aslant tract stimulation was a consequence of stimulation of U-shaped fibers that connect the superior and middle frontal gyri (Catani et al., 2012). The functional role of these fibers, both as considered on their own, and in support of the FAT, is an open question (Chernoff et al., 2018). To illustrate the proximity of these U-Fibers to the FAT in our data, Figure 1 shows tractography of the FAT as well as the U-Fibers connecting the superior and middle, and middle and inferior frontal gyri. In addition, the constraints of our task, which were motivated by the desire to elicit stereotyped responses that still required planning, adds some ambiguity that invites further consideration in future research. In particular, future research should involve the production of sentences that can differentiate between coordinate errors and errors that are specifically semantic in nature. In the context of our task, it is not clear if when the patient slipped for instance, between "triangle" and "square", whether that error constitutes a "semantic error" or rather a coordinate substitution that respects task constraints. We are developing a version of this task in which pictures of common objects and animals are used in place of geometric shapes, specifically to be able to distinguish whether lexical errors are coordinate substitutions or (proper) semantic substitutions.

It should also be emphasized that care is required when interpreting brain–behaviour relation in patients with tumours, as there may have been reorganization over a period of time as the tumour grew. This concern is assuaged by our ability to use functional MRI to localize eloquent regions in the left frontal lobe in AI that are similar in location to healthy participants. In addition, it is worth emphasizing that while AI experienced some weakness in his right foot after the surgery, his language was intact both before and after the surgery. The potential limitation associated with studying patients with brain tumours, which must be considered and managed, should not outweigh the pragmatic reality that neurosurgery patients represent the *only* opportunity to test the effects of direct electrical stimulation on language processing in the human brain.

Prior studies using direct electrical stimulation mapping have emphasized accuracy and not latency analyses (e.g., Herbet, Moritz-Gasser, Lemaitre, Almairac, & Duffau, 2018; Leonard et al., 2018; Ojemann, Ojemann, Lettich, & Berger, 1989; Orena, Caldiroli, Acerbi, Barazzetta, & Papagno, 2018; Rofes et al., 2018; Sanai, Mirzadeh, & Berger, 2008), with a few notable exceptions (e.g., Hirshorn et al., 2016). There are several reasons why caution must be exercised when using response time in the context of direct electrical stimulation, including that patients are under anesthetic agents, that the ergonomics of testing in the operating room are highly constrained, and that typically it is not possible to obtain a large number of trials during an awake craniotomy. Nonetheless, if tasks are designed with those constraints in mind, and patients sufficiently practiced so as to be able to execute the task fluently, then there is no reason why response time cannot be used to infer subtle effects of direct electrical stimulation on cognitive function. For instance, in the current investigation, the key comparison is between stimulation and non-stimulation trials, and those trials were intermixed; thus any general effects of anesthesia would affect both conditions equally. The current investigation constitutes a demonstration of the potential power of using response times to test hypotheses about underlying cognitive function using direct electrical stimulation mapping during awake craniotomies. Nevertheless, reaction time analyses must be carefully measured and due diligence is required to ensure that response times are measuring the intended aspects of patient performance (e.g., through redundancy of patient recordings in the operating rooms, careful post-processing; for further relevant discussion, Van der Linden et al., 2014; Riès and colleagues, 2012). For instance, it should be emphasized that a key component of our approach has been to optimize the quality of the audio recordings (using directional microphones) so as to be able to filter out the many extraneous background noises in the operating room.

Conclusion

Sentence production requires the integration of syntactic and phonological planning with lexical retrieval. Patients with damage to the left frontal aslant tract demonstrate an impairment in sentence production, but lexical retrieval is intact. The findings reported in this case study, together with previous related work from our group (Chernoff et al., 2018), suggest a hypothesis about why that may be the case. Future work is needed in order to integrate the SCOPE hypothesis with recent neurocognitive models of lexical access (Anders et al., 2017; Belke, 2017; Nozari & Hepner, 2018; Schnur, 2017), existing neurobiological models of speech production such as GODIVA (Bohland, Bullock, & Guenther, 2010), and network level hodotopic models of the language system (Duffau, 2015; Duffau, Moritz-Gasser, & Mandonnet, 2014). Finally, to properly evaluate the SCOPE hypothesis it will be necessary to systematically test speech fluency across a wider array of grammatical structures in the context of direct stimulation or frank injury to the frontal aslant tract.

Note

1. We are grateful to Dr. Anthony Dick for raising this possibility.

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