

Honors Thesis

HUMAN BROCA'S AREA AND NUMBERS

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ABSTRACT

Broca's Area (BA) has been the focus of extensive research. However, its functional role in articulating numbers has not been sufficiently studied. Clinical anecdotes suggest that patients with expressive Broca's type aphasia can retain the ability to verbalize numbers despite loss of speech (Dronkers et. al., 1998). In larger samples, a voxel-based lesion-symptom mapping study correlated poor performance on word tasks to BA, while number deficits correlated with parieto-temporal lobe (Piras and Marangolo, 2009).

In the current study, we seek to complement the intriguing clinical literature with controlled studies of BA during number and non-number speech. Our investigation made use of electrocorticography (ECoG) in patients undergoing routine presurgical evaluation for intractable epilepsy. Fusion of high resolution pre-op MR and post-op CT scans allowed us to precisely localize intracranial electrodes over BA in 7 right-handed subjects. We examined electrophysiological signals over neural populations in auditory, premotor, pars opercularis, pars triangularis, and pars orbitalis. Subjects repeated visually presented stimuli out loud, which either appeared in numerical form (e.g. "7" or "1"), word form (e.g. "seven" or "one"), or non-number words matched to the numbers for phonetic quality and frequency of use (e.g. "heaven" or "won").

Our findings revealed a heterogeneous pattern of electrophysiological responses in various parts of BA during articulation of different classes of stimuli. An increase in broadband gamma activity (i.e., 70-190 Hz) accompanied speech onset in some but not all BA subregions. Of these sites, a smaller subset showed preferences for one condition, usually to the word stimuli, over the others. The results indicate that neural populations in BA may be semantically selective to the numerical vs. non-numerical content of speech.

INTRODUCTION

Specific Aims

Broca's Area (BA) has been the focus of extensive research. However, its functional role in number articulation and processing has not been sufficiently studied. Clinical anecdotes suggest that patients with expressive Broca's type aphasia can retain the ability to verbalize numbers despite loss of speech (Dronkers et. al., 1998). This presents the intriguing possibility that language areas do not process numbers or process numbers separately from the rest of the lexicon. Neurological examinations however lack the necessary controls or experimental manipulations to fully test this hypothesis. Our aim was to address this question by studying the activation patterns in non-aphasic subjects during tasks involving processing of both categories of stimuli. By focusing attention on BA, a key node in language networks, the goal is to gain insight into whether a separate cognitive system handles processing of numbers, an abstraction necessary in everyday utterances and mathematical thinking. Specifically, we are interested in articulation. BA has been historically localized as a speech production center. Additionally, the clinical cases motivating this study show differences in the ability to verbalize numbers versus words in Broca's aphasics. Thus, the primary goal for this project is to compare neural activity while subjects are asked to repeat numbers or words.

Background

Paul Broca's historic 1865 paper reinforced his clinical observation from 1863 that damage to the "la troisième circonvolution frontale gauche" (third frontal convolution

lower left) led to a deficit of speech production (Broca, 1865). This was a landmark study for its success in localizing function to a brain region. Since Broca's time, the region that now bears his name has been investigated in numerous studies and has been associated in a wide variety of additional language related tasks including phonological and semantic processing, syntactic parsing, and working memory (Santi and Grodzinsky, 2007; Amunts, 2010).

Yet despite the wide range of processes Broca's Area (BA) activity has been linked to, there is evidence to suggest number and math processing are sometimes spared when other language faculties are damaged from lesions to the region. A videotaped interview of a patient with severe Broca's aphasia revealed a telling account of this phenomenon (Turkstra and Dronkers, 1993). After a middle cerebral artery infarction the patient's "productive speech consist[ed] almost entirely of the recurring utterance /tõnõ tõnõ/ (or slight variations thereof) which permeate every attempt at verbalization, including spontaneous speech, repetition, and naming" (Dronkers, Ludy, and Redfern, 1998). The investigators, however, report "knowledge of numbers is better preserved, and he often uses numbers traced in the air as part of his communication." In fact the patient is able to count from one to eleven in the video (he struggles with numbers larger than eleven and reverts back to his stereotyped utterance). While this is an intriguing case study, it presents a single data point.

There is some evidence of dissociations between number and word processing in larger patient cohorts. Investigators published a Voxel-based Lesion-symptom Mapping (VLSM) study from a group of 20 left hemisphere stroke patients (Piras and Marangolo, 2009). The patients were given a battery of tests, including a task to verbalize numbers

written as Arabic numerals (e.g. '3') or number words (e.g. 'three'), and words.

Afterward, performance on the test was analyzed in the context of each patient's voxel-based lesion map (acquired via MRI, normalized between subjects). In this type of study, when lesions in specific areas lead to deficits in specific conditions, the functions necessary to carry out that function are ascribed to that region. Brodmann's Area 44 which corresponds to cytoarchitecturally defined portion of BA, was significantly associated with deficits in the word condition, but not the Arabic numeral or number word conditions. This further supports the intriguing idea raised in the case study discussed before. Both cases show that articulation of numbers can in certain cases remain intact despite damage to BA. It is important to keep in mind, however, that the cohort included a single patient classified with Broca's aphasia.

Furthermore, another large VLSM study with 68 patients found that subjects with Broca's aphasia (n=17) tended to do significantly better in an arithmetic task to solve equations, than in a comprehension task to point to a picture matching a spoken sentence (Baldo and Dronkers, 2006). Comprehension, not arithmetic, correlated with selective impairments in Brodmann's Area 45, another area within BA. The investigators then separated out arithmetic into addition, multiplication, division, and subtraction tasks for further analysis. Addition and multiplication, perhaps as a result of being rote operations, did not yield any significant differences with comprehension. But subtraction and division yielded significant differences in Area 44 and Area 45, respectively. Their interpretation was that more computationally intensive operations were spared despite BA damage, while comprehension and more rote, memorized arithmetic tasks were not.

These lines of evidence are in accordance with a model which suggests words and numbers are handled by spatially segregated language networks, with BA as an important node for word articulation and comprehension, but perhaps not for number articulation or calculation. All of the studies cited so far are neurological surveys of patients with brain damage. Such techniques have the advantage of examining causal links between structure and function, but lack the experimental control necessary to conclusively answer the hypothesis being raised. Potential concerns include a possibility that the aphasia patients able to count numbers have simply memorized that list from repeated use. Furthermore, the lesions are not evenly distributed in all of BA, and even lesions in the same general area can affect different microstructures.

There is some work to tackle this problem with other methods from cognitive neuroscience. One group conducted a meta-analysis of 53 functional magnetic resonance imaging (fMRI) datasets involving 698 participants from various experiments for number approximation, random number generation, and arithmetic (Arsalidou and Taylor, 2011). Their conclusions confirmed involvement of the parietal and prefrontal lobes in such tasks, but only left hemisphere Brodmann's Area 44 was found to have a significant likelihood estimate in multiplication task in a single study. None of the other number and calculation related experiments showed a significant activation in BA.

An electrical brain stimulation study from a few years earlier, however, found regions within Brodmann's Area 45 were selective for verbalization of Arabic numerals and not sentences or number words (Roux et. al., 2008). Of 1,301 sites (<1 cm² cortical areas) surveyed in 53 patients, a substantial 43 sites interfered with Arabic numerals reading when stimulated. These interference sites were concentrated in three regions, including

Area 45. Unlike the other two areas of concentration (dominant inferior temporal gyrus and supramarginal gyrus) however, in BA the percentage of interferences in Arabic number reading is not significantly higher than for alphabetic script reading when intraindividual variability is taken into account. Furthermore, it is notable that the results rarely show interference of alphabetic script reading, when countless lesion and neuroimaging studies (including several reviewed above) have shown the region is necessary for speech production.

METHODS

Electrocorticography

Given the sparse and contradictory literature on number processing in BA, further research is necessary. We propose using electrocorticography (ECoG) to answer lingering questions on this subject. This alternative to traditional neuroimaging methods is possible in rare cases when intractable epilepsy patients are implanted with grid electrodes in a pre-surgical operation to determine the focus of epileptic activity. After implantation, patients rest in the hospital for several days, during which time they may participate in carefully controlled cognitive experiments. Brain activity is concurrently recorded as the patients engage in these tasks. Concerns over the quality of recordings obtained from the pathological brain are mitigated by excluding electrodes over the seizure zone, leaving healthy tissue for research analysis. The electrophysiological data obtained in this manner has a superior temporal resolution of milliseconds making it ideal for observing event related potential changes. Furthermore this electrocorticography (ECoG) method does not suffer the loss of spatial resolution evident in electroencephalography (EEG) because the electrical recordings do not pass through the insulating layer of skull (Chang et. al., 2010). This makes ECoG ideal for studying language either to examining cortical activation of a single area at a fine temporal scale (Sahin et. al. 2009) or to map networks spanning several cortical areas (Leuthardt et. al., 2012). In particular, high frequency broadband (HFB) activity (frequencies above 70 Hz) recorded over cortical regions correlates with single-neuron action potential firing and fMRI BOLD signal changes thus serving as a good measure

of cortical activation. Spatial and temporal differences in HFB activation within BA during number and word processing could generate new insight.

Electrode Coverage and Selection

In this experiment we obtained data from seven subjects implanted with grid electrodes over the inferior frontal gyrus. 5 subjects had left hemisphere coverage and 2 subjects had right hemisphere (Patient Demographic data can be found in [Table 1](#)). We used grid electrodes 1 cm apart center to center, placed under the dura in accordance with the clinical needs of the patient and verified for accuracy by fusing the pre-op MR and post-op CT scans of the subject's brains (see [Figure 1](#)). Using gross anatomical guidelines set by Keller, 2009 we classified BA in each subject. The region in the inferior frontal lobe is constrained by the inferior precentral sulcus caudally, and the inferior

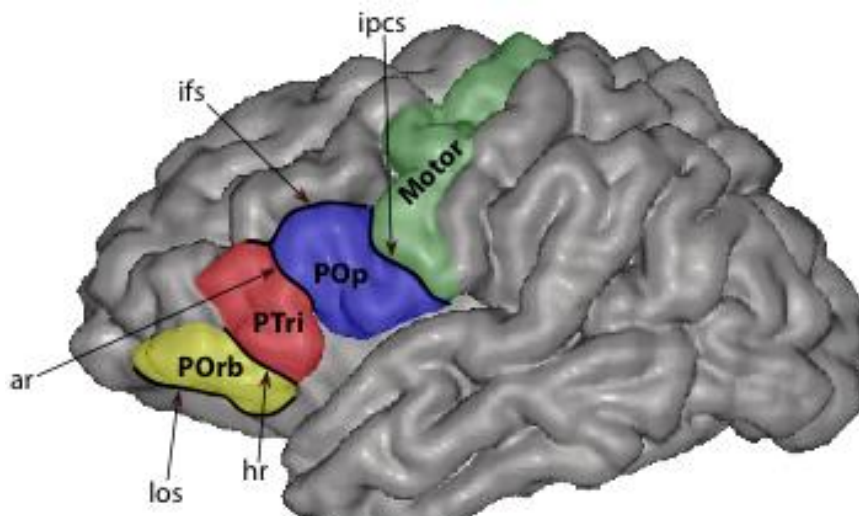
Table 1: Patient Demographic Table (* indicates Right hemisphere implantation)

Subject	Gender	Handedness	Seizure Zone	IQ
S1	M	R	L Frontal	107
S2	M	R	L Frontal	94
S3	M	R	L Frontal Temporal	88
S4	M	L	L Frontal Temporal	56
S5	F	R	L Frontal	Borderline Intellectual Functioning
S6*	M	R	R Parietal	65
S7*	F	R	R Temporal-Parietal	101

frontal sulcus dorsally. Within this region lie Pars Opercularis and Pars Triangularis, corresponding to Brodmann's Area 44 and 45. The two are separated by the ascending ramus of the Sylvian fissure. Meanwhile, the horizontal ramus of the Sylvian fissure demarcates the third area of BA, Pars Orbitalis.

Figure 1: Mesh

Reconstructed mesh of a subject's brain. Black outlines sulci (ar: anterior ramus; hr: horizontal ramus; los: lateral orbital sulcus; ifs: inferior frontal sulcus; ipcs: inferior precentral sulcus) relevant for anatomically dividing BA into the following sub-regions: Pars Opercularis (POp), Pars Triangularis (PTri), Pars Orbitalis (POrb).



Task Design

Subjects were given a simple, visually-cued word repetition task. The task was presented while the subject sat in their hospital bed looking at a closely placed laptop screen. Words in white sequentially appeared on a black background (see a schematic

of the experimental design in [Figure 2](#)). The task had been designed on MatLab using Psych Toolbox. The subject was instructed to say the word out loud into a microphone. The next stimuli initiated when the subject finished speaking, and the experimenter pressed a keyboard button. 60 randomly interspersed stimuli will be presented in each experiment, consisting of 20 numbers represented in numeral form (Number condition, e.g. '7'), written out (Number Word condition, e.g. 'Seven'), and 20 words that phonetically similar to the numbers (Word condition e.g. 'Heaven'). Controlling for the phonetic similarity will isolate differences between categories to semantics (see [Table 2](#) for a complete list of all stimuli).

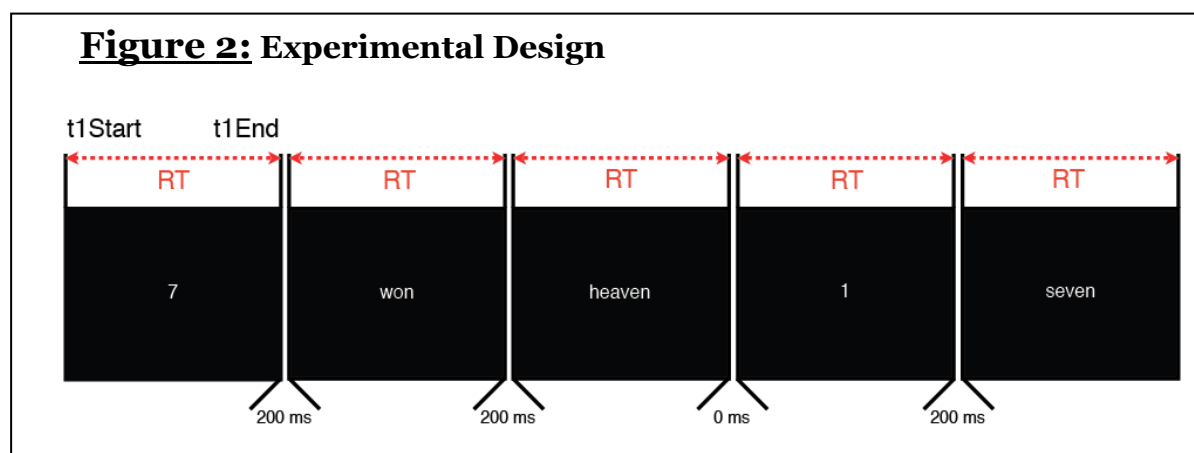


Table 2: Stimuli List

Number	Number Word	Word
8	eight	aid
11	eleven	celebrate
50	fifty	dirty
5	Five	elephant
40	forteen	for
4	forty	fortress
14	four	heaven
9	nine	hero
90	ninty	hive
1	one	nauty
7	seven	nifty
16	six	pine
6	sixteen	plenty
10	ten	sex
30	thirty	shorty
3	three	sustain
20	twenty	thin
28	twenty eight	too
2	Two	tree
0	zero	won

Data Analysis

Two types of data were collected from this experiment. First, behavioral data included the photodiode and microphone files indicated the onset of stimuli and speech, respectively. Second, electrophysiological data from the grid electrodes was collected. The raw neural data during the task was compressed (decimated by compression rate), filtered (bandpass filter for 60 Hz noise, and its harmonics: 120, 180, etc.), and common average referenced (subtract the mean from the activity in each electrode, average this activity across electrodes to obtain the Common Average Reference, and finally subtract each electrode from this CAR). Then a Fourier transform was applied (Discrete

Fourier Transform (DFT) to go from time domain to frequency domain using a Fast Fourier Transform (FFT)); the signal was band pass filtered to each frequency band (log-spaced apart from 1-250 Hz); and finally a Hilbert transform was applied to find the amplitude and phase at each point. For analyzing in discrete bands, FFT was not used, instead the signal in the time domain is decimated, band pass filtered according to preset frequency bands and finally passed into a Hilbert transform. Our analysis primarily looked at the HFB power, which was the square of the amplitude in the 70-190 Hz range.

By listening to and visually examining the audio trace of the subject's responses from the microphone file, we time stamped the onsets of speech following each stimulus. These trials belonged to one of the three categories. We could then examine the HFB activity electrode by electrode over a time window surrounding speech onset. Such windows were created around each trial, and averaged together for trials of the same condition in order to create bar graphs for each condition.

In order to normalize the raw HFB, a surrogate distribution was also compiled for each electrode. Each surrogate was the same length of time as a trial, but the window centered on a random time point from the experiment rather than the speech onset. Furthermore, since a period of quiet activity did not precede speech as a baseline measure, taking a surrogate distribution to compare with was better suited to the experimental design. To simulate experimental conditions, the same number of random surrogate trials was selected as the number of experimental trials. Thus averaging over the time surrounding the trials created a window comparable to the condition. Then to create a distribution, this selection was repeated 235 times ([Figure 3](#)). This resampling

method kept the structure of the conditions and accurately reflected the global variance in HFB power over the experiment. But the windows were not time locked to a condition or speech onset.

The averaged window for each condition could then be subtracted against the mean and standard deviation of the surrogate distribution to obtain a normalized value. The Z-statistic obtained indicated the level of activation above the baseline. If any experimental condition activated the electrode, we expected Z-scores greater or less than one half standard deviations from the mean ($p < 0.30$).

The electrodes that showed some sign of activity from above were then analyzed for differences between experimental conditions. An ANOVA was run between trials of each condition. Tukey's post-hoc test was run if significant differences were discovered.

RESULTS

Verification of Methods in Visual Cortex

First, we wished to validate our data analysis in a control electrode with predictable properties. An electrode over the primary visual area was the clear choice, as we expect immediate, strong activation when a stimulus is appears on screen. Furthermore, such a low level visual area is not likely to be tuned to differences between the conditions used in this experiment. Although most subjects with electrodes placed over the lateral frontal lobe do not simultaneously have coverage in caudal brain regions, Subject 7 did have a strip of electrodes reaching the occipital lobe. We analyzed an electrode over what appeared to be a primary visual area. The pattern of activation is shown in [Figure 4](#). The properties of this electrode confirmed the null hypothesis. First, we observed the electrode was active following the stimulus, according to our criteria of half standard deviation above or below the baseline surrogate mean. Second, an ANOVA revealed no significant difference between the Word, Number Word, and Number conditions.

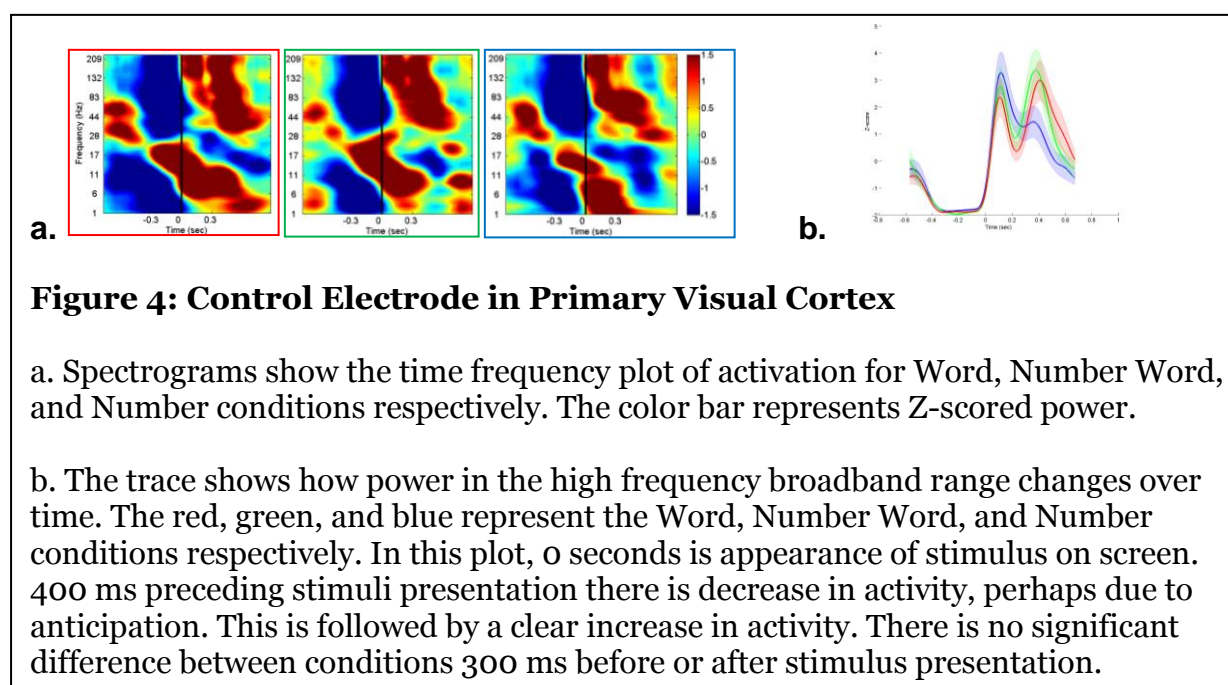


Figure 4: Control Electrode in Primary Visual Cortex

a. Spectrograms show the time frequency plot of activation for Word, Number Word, and Number conditions respectively. The color bar represents Z-scored power.

b. The trace shows how power in the high frequency broadband range changes over time. The red, green, and blue represent the Word, Number Word, and Number conditions respectively. In this plot, 0 seconds is appearance of stimulus on screen. 400 ms preceding stimuli presentation there is decrease in activity, perhaps due to anticipation. This is followed by a clear increase in activity. There is no significant difference between conditions 300 ms before or after stimulus presentation.

Response in Broca's Area to Speech

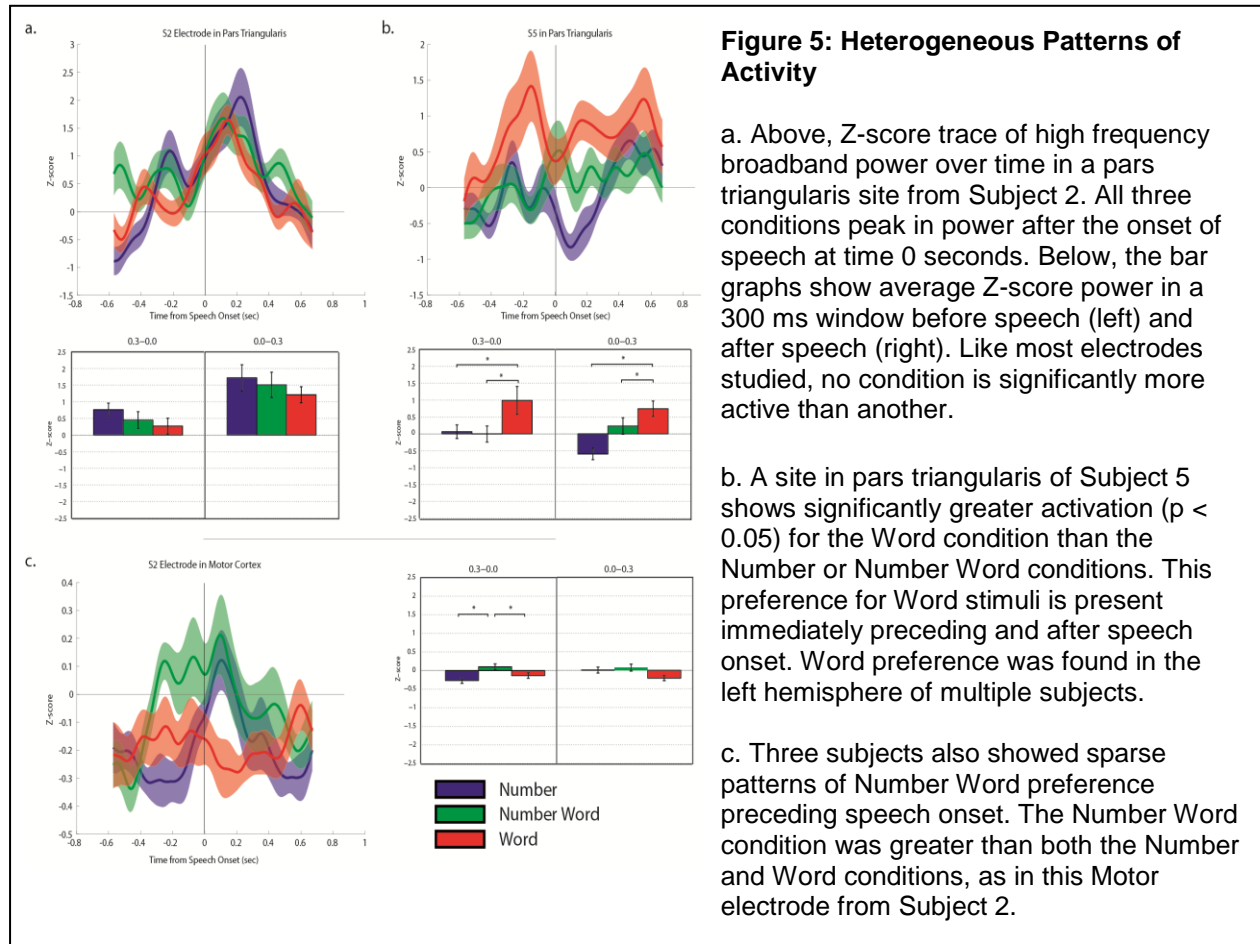
Thus with confidence in our method of analysis, we were able to examine electrodes in areas of greater interest to our study. First we combed through all anatomically selected electrodes in BA, motor, and auditory cortex for electrodes to remove epileptic and noisy channels. Motor and auditory electrodes were included to serve as controls. We expect activity in these areas as well, when the subject moves muscles to articulate and hears his or her own voice. Of 172 total electrodes across the seven subjects, 106 left hemisphere and 37 right hemisphere electrodes were fit for analysis. All of our analysis was in the 70-190 Hz, high frequency broadband range, which has been shown to relate to activity at the level of neural spiking. Less than one third of the electrodes were active during a 600 ms period surround speech onset. There were only two instances of below baseline activity in the left hemisphere. Meanwhile, 38 electrodes showed above baseline activity in left hemisphere, particularly concentrated in Pars Opercularis, Pars Triangularis, and motor cortex. BA in Subjects 3 and 4, however, appeared inactive. We will speculate on potential right dominance of language function in these individuals later in this paper. We noted activation often preceded speech onset, finding just as many electrodes active in the 300 ms region preceding speech as the 300 ms after. In right hemisphere subjects, we found an equal number of above and below baseline active electrodes. However the topographic distribution of these electrodes was different. Above baseline electrodes were almost exclusively in auditory or motor cortices, while below baseline electrodes were in BA. This observation agrees with our understanding of the lateralization of language. While auditory and motor areas

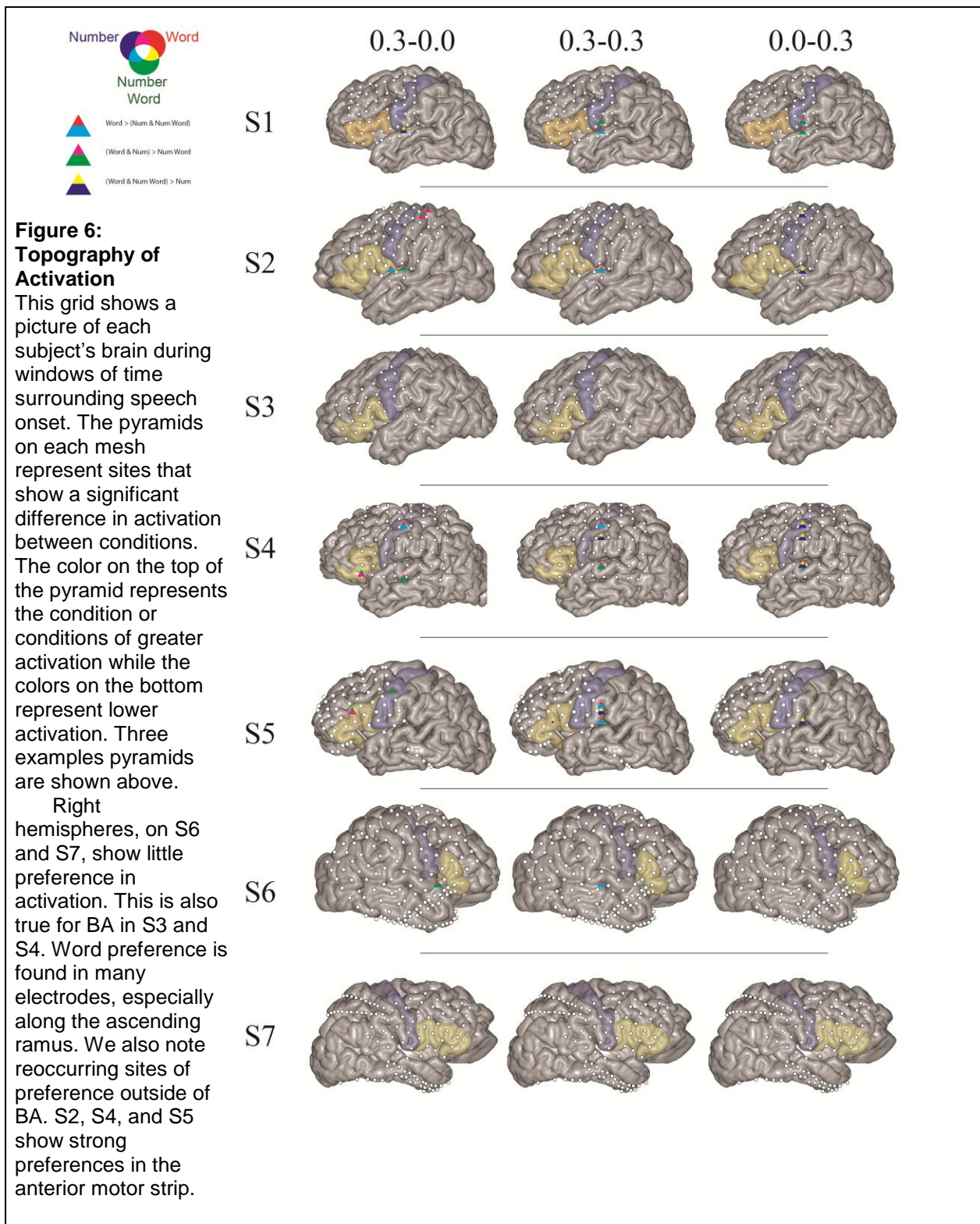
on both hemispheres are necessary to verbalize and listen, the right hemisphere counterparts to language areas on the left are not involved with this cognitive process.

Preferences to Conditions

The active electrodes were selected for further study. In this limited subset, we tested the null hypothesis that high frequency broadband power between conditions is the same. Many sites indeed showed no preference (see [Figure 5a](#)). This was especially true in the right hemisphere. Only one electrode in the auditory cortex of this hemisphere showed a stronger response to Numbers and Words over Number Words. Even most active electrodes in the left hemisphere displayed no differences between conditions. However, we also found electrodes which rejected the null hypothesis. These sites were spatially distributed, including electrodes in Pars Triangularis and Motor cortex in several subjects ([Figure 5b](#)). Most of these electrodes showed the Word condition dominating in power over one or both of the other conditions. In fact, one or more electrodes in BA of every subject would have exhibited a Word preference; however, in S3 and S4 the electrodes displaying this preference did not meet the criteria for active. We found evidence of dissociations between verbalizing words and numbers, words and number words, and number words and numbers. Four electrodes in different areas in three left-hemisphere subjects had an alternate preference to Number Word, over both Words and Numbers, before the onset of speech ([Figure 5c](#)). No electrode displayed this property during speech. Though this was a smaller set, it established an important example of a combined orthographic-semantic tuning. We did not, on the other hand, discover any electrodes with a preference for Numbers. Though finding Word preference in BA electrodes was foreshadowed by the clinical literature, we found

it surprising to see preferences for these conditions in many motor and a few auditory areas. The spatial distribution of preference can be seen in [Figure 6](#). Sites in anterior motor strip displayed preferences between conditions in three out of the five left hemisphere subjects, including two of the four Number Word preferring electrodes.





DISCUSSION

In this study, our aim was to further investigate clinical leads on number processing in BA. We specifically examined the production of Words, Number Words, and Numbers. The high frequency broadband power was quantified before, during, and after speech in anatomically relevant electrodes. Our results demonstrated the incredible heterogeneity of BA. Classically recognized for its role in language production, we found only about a third of the electrodes examined were responsive during speech. Of these, most electrodes showed no difference between conditions in their anatomical location.

Some spatially distributed sites in BA, motor, and auditory cortices did show preferences to one or two conditions over the rest. In particular, the Word condition was found to selectively activate several electrodes in the left hemisphere both immediately before and after speech. Lesions through these areas could disrupt word verbalization while sparing the patient's ability to articulate other linguistic forms. Such lesions through selective Word regions in BA may have been the diagnosis of the aphasic patient observed by Turkstra and Dronkers.

Because numbers must be articulated as well, we may have been surprised at the lack of Number selective counterparts. However, voxel-based lesion-symptom mapping studies (Piras and Marangolo, 2009) and cortical microstimulation (Roux et. al., 2008) studies have shown Number preferring areas are located in temporo-parietal areas, which were not included in this study.

Initially, it seems peculiar that to have found Number Word preference at all in a verbalization task. Orthographic differences in writing are not expected to have an effect on language production. Standard models suggest that the written form is transformed

into some sort of internal representation before being spoken, and thus the articulation of '7' and 'seven' would be expected to originate from the same representation. Note, however, all preferences for Number Word were found before the onset of speech and never after, perhaps indicating activity for Number Word was involved in reading and creating a mental representation, not speech. This would be reasonable, as number words are a unique semantic-orthographic combination compared to the other two conditions.

The topographic distribution of word preference does not allow us to conclude a specific subregion of BA is the most involved in selectively processing linguistic categories. However, we note a trend: Sites active preferentially to the Word condition seem common along the ascending ramus of the Sylvian fissure, especially along the side of Pars Triangularis. The four left hemisphere subjects with active BA indeed had Word preference sites along this ramus. The nature of electrode recordings allows limited areas of the cortical surface to be studied in each subject. Extending this study in the future, additional points can be surveyed to determine whether Pars Triangularis truly does exhibit greater Word preference than neighboring regions.

While BA was suspected to have preference for certain linguistic categories, this was not expected in lower cognitive areas. However, we found such effects across several subjects. In fact, the only site that showed differences between conditions in the Right hemisphere was an auditory electrode in S6. More notably, motor electrodes were strongly active, and many displayed category preference. Two of the four electrodes with Number Word dominance were in the motor strip, for instance. While we expected only motor electrodes close to BA to be active (from where on the homunculus the vocal

cords and mouth muscles are controlled), anterior electrodes showed strong asynchronous activation between conditions. We speculate this region's proximity to the parietal lobe, which has known roles in numerical cognition.

Finally, two subjects exhibit unusually quiet BA during speech production. Almost no electrodes meet the liberal criteria for being considered active: half standard deviation above or below the surrogate mean. These subjects are able to communicate, meaning the language related response must be present somewhere else. In a small percentage of the population, there is a shift in language function from the left to the right hemisphere. We believe this may be the case for S3 and S4. Separate microstimulation experiments, conducted in the clinic when seizure mapping, show no speech arrest in these subjects when BA is stimulated. Without electrode coverage on the right hemisphere, we are unable to conclude this for certain, but the quiet BA combined with the null effects of stimulation in the left hemisphere strongly point to this conclusion. Thus it is worth considering that trends noticed in BA in other Left hemisphere subjects may not apply to these two.

The results of this experiment suggest to us that different networks underlie language processing in BA. These networks are separated based on semantic and orthographic properties. Some networks or parts of networks are invariant to these properties, while others exhibit preferences between different linguistic representations. Numbers and words are indeed separated when processing numbers, not just at the stage of BA but also in some parts of auditory and motor processing. Further experiments will reveal whether these differences hold in the case of number based cognition, such as numerosity or arithmetic.

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