Structural Connectivity of Language and Motor Areas
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Abstract

To further understand language, this exploratory study attempted to corroborate previous findings indicating a functional connectivity between Broca's Area (BA 44/45), the primary speech production region, and the Premotor Cortex (BA 6), involved in motor planning, with High Definition Fiber Tracking. By processing and analyzing Magnetic Resonance Imaging data from five healthy, right-handed male subjects, six regions of overlap from BA 44/45 and BA 6 were identified and classified based on trends in the data. This indicates that there are intermediate regions identifiable from diffusion data to suggest a functional connectivity between language and motor.

Introduction

Speech production is a crucial part of language. It has long been understood that the speech production part of the brain is contained in Broca's area, also known as Brodmann's Areas 44 and 45 (Ford *et al.*, 2010). Studies have shown that a functional connectivity exists between Broca's Area and the areas projecting directly to the premotor cortex, located at Brodmann Area 6 (Ford *et al.*, 2010). The premotor cortex is involved in motor planning and connects to the primary cortex; Broca's Area relays the signal of mouth movement to BA 6, which also relays to the primary motor cortex for speech production.

One study observed the activation of both the ventral premotor cortex and a region homologous to Broca's Area in monkey models during vocalization (Coude *et al.*, 2011). The study further concluded that the human ventral premotor cortex and Broca's Area are implicated in voluntary speech, indicating a functional connectivity (Coude *et al.*, 2011). A further study attempted to find a structural connectivity between Broca's area and Brodmann's Area 6 (Ford *et al.*, 2010). Using MRI scans and fiber tractography, the study was able to find correlations that suggested structural connectivities between Broca's Area and Brodmann's Area 6 and 9 (Ford *et al.*, 2010). The aim of this present study was to corroborate the findings in the Ford *et al.* study using the High-Definition Fiber Tracking method.

Finding a structural connectivity between Broca's Area and the Premotor Area would confirm that language and motor pathways are not just functionally linked. A structural connectivity also suggests mirror neuron involvement (Rizzolatti, Arbib, 1998): In the early 1990s, there was a fascinating discovery involving a specific set of neurons,

later called mirror neurons because of their imitative properties, that have been recently implicated with language. Mirror neurons, a subset of the visuomotor system, are fired in one subject during observation of some action in another subject, suggesting an understanding of intention by the observer. We suggest that the relation of language to mirror neurons involves the hand motor cortical area, since gestural movement seems to be implicated in language evolution. There has been data showing a connection between the cortical brain regions for hand movement and language such that reading aloud and spontaneous speech increase excitability of dominant hand motor regions compared to rest (Meister *et al.*, 2003). Furthermore, this study found that silent reading did not influence the excitability of hand motor regions, additionally supporting the connection between speech and hand motor (Meister *et al.*, 2003).

Methods

Subjects

Five healthy, control subjects--right-handed males aged 22-36--were recruited for this study (T1, T2, T4, T6, WILL). Subjects participated in Magnetic Resonance Imaging to procure T1 structural data which led to Diffusion Spectrum Imaging data compatible with the High Definition Fiber Tracking methods.

High Definition Fiber Tracking

An imaging method created by researchers at the University of Pittsburgh which takes Diffusion Spectrum Magnetic Resonance Imaging data and partitions the white-gray matter into Regions of Interest to create a network construction that can be used to create white matter tractography (Hagmann *et al.*, 2007).

Regions of Interest and Analysis

All regions of interest were identified using the Brodmann Area (BA) system of cortical organization of the brain. According to previous studies, the Premotor Cortex is located within Brodmann Area 6 whereas the Broca's Area spans across Brodmann Areas 44 and 45. The current study used the computer program "DSI Studio" which contained pre-defined regions for each Brodmann Area.

BAs 44 and 45 were merged together to form a single ROI. Furthermore, each BA was "dilated" (Keyboard command Control + D) in order to standardize the preset regions to control for interindividual variations and selected to only represent one hemisphere at a time. In addition to these four sphere ROI's (bilateral BA 44/45 and BA 6) was a

mid-sagittal Region of Avoidance (ROA) which was inserted to avoid interhemispheric crossing (*Figure 1*).

In each control subject, preliminary global seeding was conducted with each of the four ROI's (used as "ends") and the ROA(*Figure 2 & 3*). From qualitative analysis and observation, six regions of overlap were identified and matched to pre-existing Brodmann Areas (*Figure 4*). An area of overlap was self-defined if more than ten end projections from both the BA 44/45 and BA 6 were present. Each of these six regions was then separately cast as an End ROI with both the BA 44/45 End ROI and BA 6 End ROI,the mid-sagittal ROA, and then tracked.

The tracking parameters for each brain were fairly consistent with only the threshold being manipulated to match each subject. The fiber tracking parameters used were as follows:
- Angular Threshold: 80
- Step Size: 0.5 mm
- Smoothing: 0.2
- Length Constraints: 20 mm-200 mm
- Seeds: 200,000 Global
- QA Threshold: T1 (0.0400), T2 (0.0470), T4 (0.0380), T6 (0.0450), WILL (0.0350)

Variable QA thresholds were used for each subject to maximize Orientation Diffusion Function (ODF) data. The selected threshold was based on the appearance of voxel contiguity for each subject's white matter structural images. After the program generated the tracts, interhemispheric crossings were trimmed (negligible because of placement of the mid-sagittal ROA). The remainder of the tracts were analyzed for streamline count which was averaged across brains for each hemisphere and from each origin of projection (BA 44/45 or BA 6) (*Table 1*). The standard deviations and percentage of streamlines to each respective category (hemisphere and origin of projection) were calculated for each area of overlap identified (Figure 1).

Results

Six areas of overlap were found: BA 9, 20, 22, 37, 39, and 40. Three types of streamline trends were observed: lateralization, region projecting tendency, and region interactions. Lateralization was defined as one region receiving more connections from both the Premotor Cortex and Broca's Areas on one hemisphere, or overlap, than the other hemisphere. If 65% or more of the total projections to a BA connected to one hemisphere, this hemisphere was defined as lateralized. A Brodmann Area of overlap

was also observed to have more overall projections to both hemispheres from either the Premotor Cortex or Broca's Area, referred to as region projecting tendency. Region interactions occurred when two areas of overlap had strikingly similar lateralization and tendency trends. Projection percentages were calculated for each overlapping region by dividing the streamline count of a projection area-hemisphere pair with the total number of streamlines in that overlapping region. Complete results can be seen in Table 1 and Chart 1.

Lateralization (*Figure 5*)

BA 20 and BA 37 were left-lateralized while BA 39 and BA 40 were right-lateralized.

BA 20 is known as the inferior temporal, fusiform, and parahippocampal gyri (The University of Texas Medical School at Houston, 2015). 78% of the total projections to BA 20 in both hemispheres projected to the left hemisphere. 34.3% of the total projections were from the Premotor Area while 43.7% was from Broca's Area.

BA 37 is known as the posterior inferior temporal, middle temporal, and fusiform gyri (The University of Texas Medical School at Houston, 2015), had 71.7% of its total projections going to the left hemisphere. 28.2% of the total BA 37 projections were from Broca's area to the left hemisphere. 43.5% was from the Premotor Area to the left BA 37.

BA 39 is known as the angular gyrus (Caspers, 2008). 70.8% of all the projections to BA 39 bilaterally projected to the right hemisphere.

BA 40 is known as the supramarginal gyrus (Caspers, 2008). 68.6% of total bilateral streamlines to BA 40 from the Premotor and Broca's Areas projected to the right hemisphere.

Region Projecting Tendency (*Figure 6*)

BA 9 and BA 22 both had more overall projections from Broca's Area to both hemispheres.

BA 9 is known as the dorsolateral prefrontal cortex (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997), received 76.6% of its projections from Broca's Area.

BA 22 is known as the Wernicke's Area (Dubuc, 2015), received 73.2% of its total projections from Broca's Area.

Region Interactions (*Figure 7*)

BA 39 and BA 40 had very similar streamline trends, in addition to both being right-lateralized.

In the right hemisphere, Broca's area and the Premotor Cortex had almost equal contribution. 70.8% of the total projections to BA 39 were to the right hemisphere: 37.9% of the total projections were from the Premotor Area, while Broca's Area contributed 32.9%. 68.6% of the total number of streamlines to BA 40 were to the right hemisphere: the Premotor Cortex contributed 34.4% to the right BA 40 while 34.2% of the projections originated in Broca's Area.

In the left hemisphere, the Premotor Cortex contributed more streamlines than Broca's area did. 25.9% and 24.4% of the total bilateral projections were from the premotor area to the left BA 39 and 40, respectively. Of the total bilateral projections to BA 39, only 3.3% were from Broca's area to the left hemisphere. This percentage in BA 40 was 7.0%.

Discussion

Key Findings

The key finding is that healthy, right-handed male control subjects consistently have regions of overlapping projections from both the Premotor Cortex and Broca's Area. Six regions were identified across five subjects, some of which had more streamlines counts in the left or right hemisphere. This was not an expected result as it was hypothesized that the left hemisphere would consistently have more streamline projections since it has been implicated with language in previous literature (Dubuc, 2015). Some of these regions received more projections from either the Premotor Cortex or the Broca's Area, also determined by comparing streamline counts. A third pattern noticed was an interaction between the hemispheric lateralization and the Premotor Cortex or Broca's Area projection tendency.

Implications

According to past studies, there are several explanations for the observed trends in streamline count:

Lateralization
BA 20 and BA 37 on the left hemisphere both received more projections from the Premotor Cortex and Broca's Area than on the right. These areas are a part of the Visual-Temporal System where BA 20 is the Inferior Temporal Gyrus and BA 37 the Posterior Inferior and Middle Temporal Gyrus (The University of Texas Medical School at Houston, 2015). These gyri have been implicated with processing the visual properties of objects, connecting to other regions responsible for assigning proper

names (Aboitiz & Garcia, 1997). Also housed in BA 37 is the Fusiform Gyrus, also implicated with word recognition (Nobre & McCarthy, 1994). Furthermore, lesions in these regions have been shown to lead to agraphia, or impairments in spelling (Rapcsak & Beeson, 2014). The left-lateralization of these areas, involved mostly with language, supports the left-lateralization of most language in the literature (Dubuc, 2015).

BA 39 and BA 40 received more projections on the right hemisphere than the left. This observation contradicts existing literature about language areas being left-lateralized (Dubuc, 2015). One possible hypothesis suggests that the left-lateralization of language is not universal. In fact, 5% of the right-handed population has a right-lateralized language area (Dubuc, 2015). Perhaps the subjects in this data set belonged to this 5%, but this supposition is not conclusive.

Region Projecting Tendency
BA 9 and BA 22 tend to receive more projections from the Broca's Area as opposed to the Premotor Cortex, regardless of the hemisphere. Bilateral activation of BA 9, also called the Dorsolateral Prefrontal Cortex, has been linked to higher scores on the Raven's Progressive Matrices test, an accepted measurement of fluid intelligence (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997). BA 9 also seems to be one site for non-literal, idiom processing, a higher level language ability, as marked by the difficulty of acquisition for non-native speakers (Romero, Tettamanti, Cappa, & Papagno, 2008). BA 22, or the Wernicke's Area, is implicated with language comprehension, connected to the Broca's Area by means of the Arcuate Fasciculus, the primary language fiber tract (Dubuc, 2015). Whereas the Broca's Area more or less is responsible for language production, the Wernicke's Area aids in language comprehension for a "representation of phonemic sequences" (Duboc, 2015). The observed tendency for these regions to receive more projections from the Broca's Area as opposed to the Premotor Cortex corroborates past findings that implicate these areas with language.

Region Interactions
BA 39 and 40, in addition to being right-lateralized, had very similar streamline trends overall. Together, BA 39 and BA 40 make up the inferior parietal lobule (Caspers, 2008), implicated in the semantic processing of language (Dubuc, 2015). This observation makes sense intuitively because BA 39 and 40 (*Figure 4*) are in close proximity to Wernicke's Area, known for language comprehension. The similarities in streamline trends reflect that BA 39 and 40 act as one entity for language processing.

Constraints

A major constraint for this study was the small sample size. Because the subject pool was restricted and there were several conditions that subjects had to meet (handedness, age), there was not enough access to a large sample. Similarly, because the duration of this project was just a couple of weeks, there was not enough time to go into any deeper analyses with the data than what is presented. Finally, due to a general lack of concurrence in the neuroscience community of naming regions, locating specific features, and determining functions, other studies may draw contrasting conclusions to what the present study suggests.

Future Research

Understanding the areas of overlap between the Premotor Area and Broca's Area would allow further investigation of the effects of handedness on language and the involvement of mirror neurons in language. The effect of trauma to the brain could also be predicted by mapping the connections between language and motor areas. Lastly, this study gives way to a new method of aphasia analysis.

Tables

Table 1: Streamline Counts and Averages
*Averages shown in boxes underneath Streamline Count.

Left Hemisphere				
Area of Interest	**Subject**	**Projection Region**	**Streamline Count**	
BA 9	T1	Broca Area	869	1024
BA 9	T2	Broca Area	450	607
BA 9	T4	Broca Area	200	148
BA 9	T6	Broca Area	83	139
BA 9	WILL	Broca Area	361	378
			425.9	
BA 9	T1	Premotor Cortex	23	50
BA 9	T2	Premotor Cortex	79	98
BA 9	T4	Premotor Cortex	64	44
BA 9	T6	Premotor Cortex	20	11
BA 9	WILL	Premotor Cortex	245	237
			87.1	
BA 20	T1	Broca Area	410	414
BA 20	T2	Broca Area	259	215
BA 20	T4	Broca Area	46	23
BA 20	T6	Broca Area	191	217
BA 20	WILL	Broca Area	90	79
			194.4	
BA 20	T1	Premotor Cortex	433	336
BA 20	T2	Premotor Cortex	253	214
BA 20	T4	Premotor Cortex	41	21
BA 20	T6	Premotor Cortex	92	82
BA 20	WILL	Premotor Cortex	24	27
			152.3	
BA 22	T1	Broca Area	9	8
BA 22	T2	Broca Area	3	21
BA 22	T4	Broca Area	12	8
BA 22	T6	Broca Area	11	8
BA 22	WILL	Broca Area	11	7
			9.8	
BA 22	T1	Premotor Cortex	3	4
BA 22	T2	Premotor Cortex	19	4
BA 22	T4	Premotor Cortex	12	4
BA 22	T6	Premotor Cortex	2	4
BA 22	WILL	Premotor Cortex	4	0

			5.6	
BA 37	T1	Broca Area	5	3
BA 37	T2	Broca Area	119	75
BA 37	T4	Broca Area	68	32
BA 37	T6	Broca Area	21	14
BA 37	WILL	Broca Area	169	85
			59.1	
BA 37	T1	Premotor Cortex	69	55
BA 37	T2	Premotor Cortex	151	126
BA 37	T4	Premotor Cortex	141	87
BA 37	T6	Premotor Cortex	32	36
BA 37	WILL	Premotor Cortex	134	81
			91.2	
BA 39	T1	Broca Area	2	3
BA 39	T2	Broca Area	13	4
BA 39	T4	Broca Area	1	1
BA 39	T6	Broca Area	5	2
BA 39	WILL	Broca Area	6	4
			4.1	
BA 39	T1	Premotor Cortex	43	15
BA 39	T2	Premotor Cortex	106	27
BA 39	T4	Premotor Cortex	23	1
BA 39	T6	Premotor Cortex	26	20
BA 39	WILL	Premotor Cortex	50	16
			32.7	
BA 40	T1	Broca Area	60	21
BA 40	T2	Broca Area	1	1
BA 40	T4	Broca Area	19	9
BA 40	T6	Broca Area	0	0
BA 40	WILL	Broca Area	8	8
			12.7	
BA 40	T1	Premotor Cortex	83	40
BA 40	T2	Premotor Cortex	81	64
BA 40	T4	Premotor Cortex	60	7
BA 40	T6	Premotor Cortex	26	14
BA 40	WILL	Premotor Cortex	53	8
			43.6	

Right Hemisphere				
Area of Interest	**Subject**	**Projection Region**	**Streamline Count**	
BA 9	T1	Broca Area	440	417
BA 9	T2	Broca Area	309	374
BA 9	T4	Broca Area	158	133
BA 9	T6	Broca Area	165	273
BA 9	WILL	Broca Area	200	259
			272.8	
BA 9	T1	Premotor Cortex	272	230
BA 9	T2	Premotor Cortex	39	26
BA 9	T4	Premotor Cortex	135	169
BA 9	T6	Premotor Cortex	31	28
BA 9	WILL	Premotor Cortex	211	132
			127.3	
BA 20	T1	Broca Area	22	7
BA 20	T2	Broca Area	136	93
BA 20	T4	Broca Area	46	35
BA 20	T6	Broca Area	94	99
BA 20	WILL	Broca Area	1	1
			53.4	
BA 20	T1	Premotor Cortex	0	5
BA 20	T2	Premotor Cortex	94	105
BA 20	T4	Premotor Cortex	15	13
BA 20	T6	Premotor Cortex	143	72
BA 20	WILL	Premotor Cortex	0	0
			44.7	
BA 22	T1	Broca Area	28	29
BA 22	T2	Broca Area	12	7
BA 22	T4	Broca Area	9	5
BA 22	T6	Broca Area	13	4
BA 22	WILL	Broca Area	0	0
			10.7	
BA 22	T1	Premotor Cortex	0	2
BA 22	T2	Premotor Cortex	3	2
BA 22	T4	Premotor Cortex	4	4
BA 22	T6	Premotor Cortex	4	0
BA 22	WILL	Premotor Cortex	0	0
			1.9	

BA 37	T1	Broca Area		69	68
BA 37	T2	Broca Area		17	10
BA 37	T4	Broca Area		18	27
BA 37	T6	Broca Area		50	50
BA 37	WILL	Broca Area		7	3
			31.9		
BA 37	T1	Premotor Cortex		13	22
BA 37	T2	Premotor Cortex		6	7
BA 37	T4	Premotor Cortex		3	10
BA 37	T6	Premotor Cortex		120	87
BA 37	WILL	Premotor Cortex		5	3
			27.6		
BA 39	T1	Broca Area		83	103
BA 39	T2	Broca Area		21	39
BA 39	T4	Broca Area		3	44
BA 39	T6	Broca Area		5	8
BA 39	WILL	Broca Area		39	69
			41.4		
BA 39	T1	Premotor Cortex		71	73
BA 39	T2	Premotor Cortex		31	65
BA 39	T4	Premotor Cortex		0	7
BA 39	T6	Premotor Cortex		33	83
BA 39	WILL	Premotor Cortex		15	99
			47.7		
BA 40	T1	Broca Area		101	67
BA 40	T2	Broca Area		73	99
BA 40	T4	Broca Area		22	75
BA 40	T6	Broca Area		3	0
BA 40	WILL	Broca Area		66	106
			61.2		
BA 40	T1	Premotor Cortex		60	96
BA 40	T2	Premotor Cortex		48	29
BA 40	T4	Premotor Cortex		37	119
BA 40	T6	Premotor Cortex		29	22
BA 40	WILL	Premotor Cortex		85	90
			61.5		

Figures

Figure 1: ROI Placement
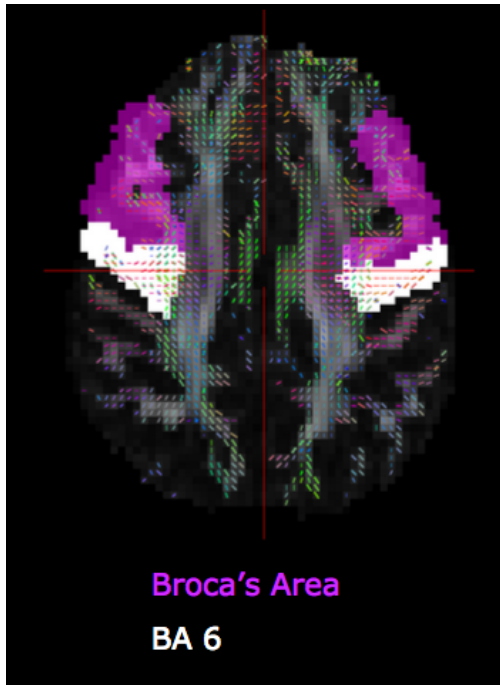
Figure 2: Projections from Broca's Area and Premotor Cortex to Region of Overlap
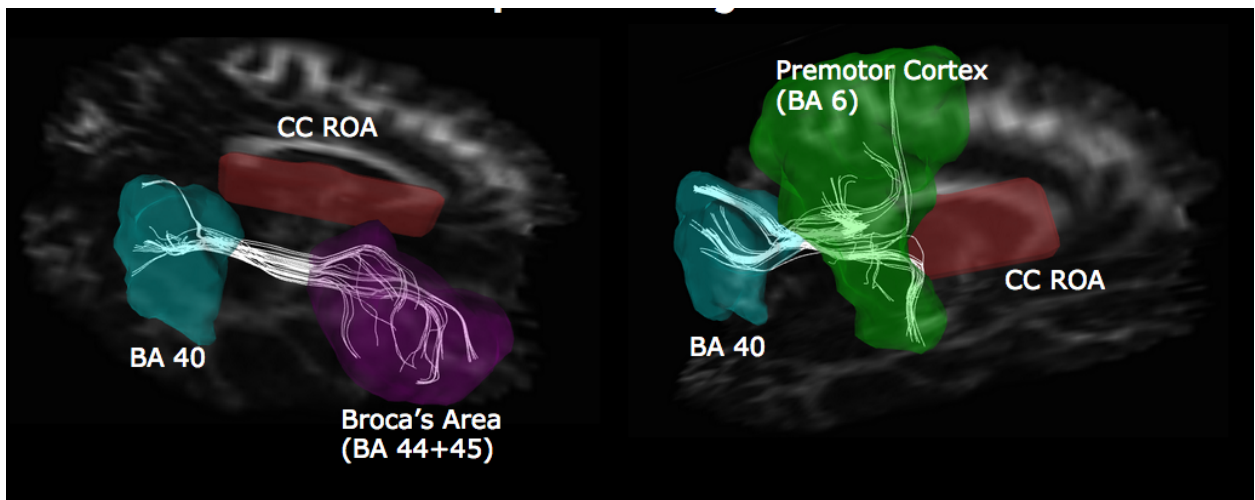
Figure 3: Example of Region of Overlap
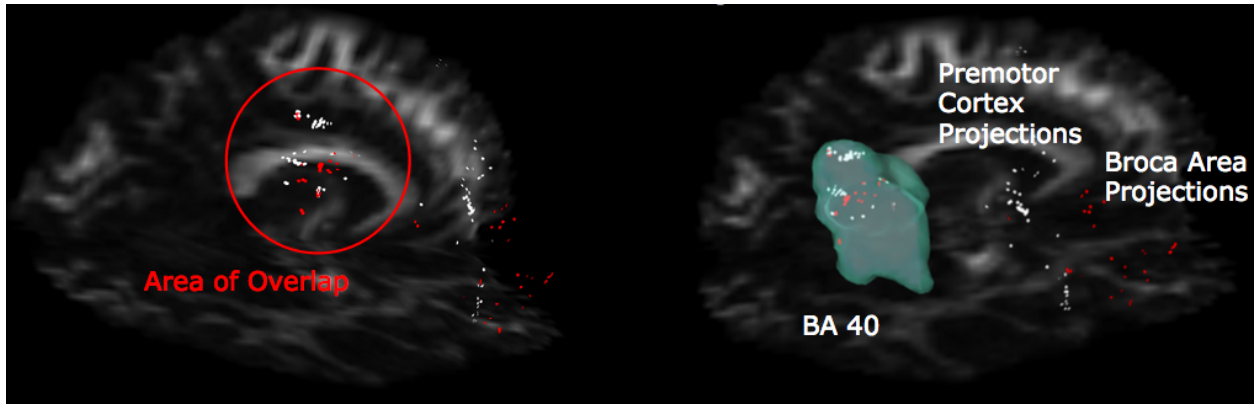
Figure 4: Identified Regions of Overlap
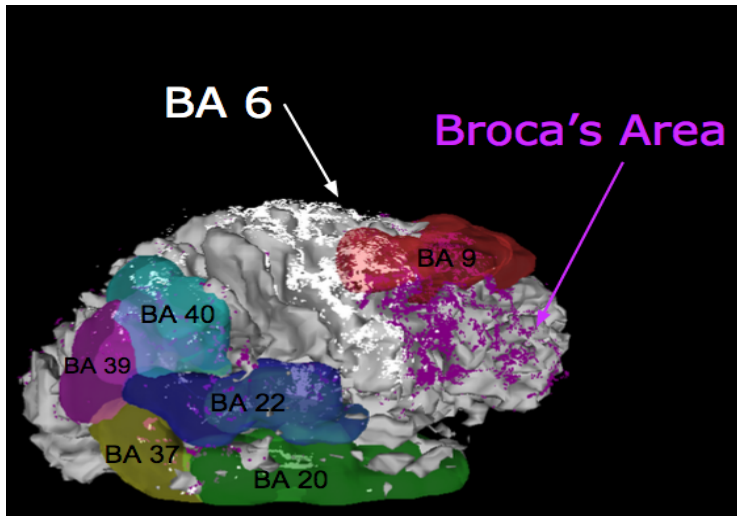
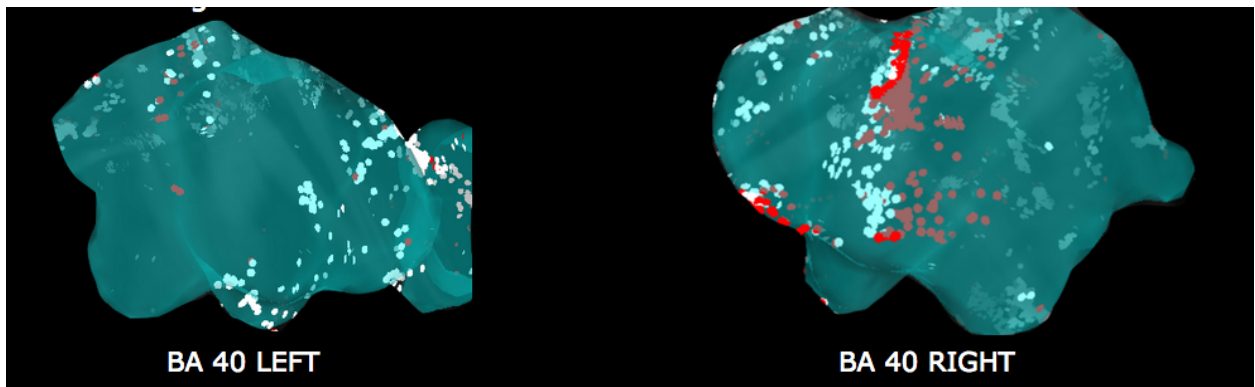*Figure 5: Example of Lateralization(Red-Broca Projections, White-Premotor Projections)*
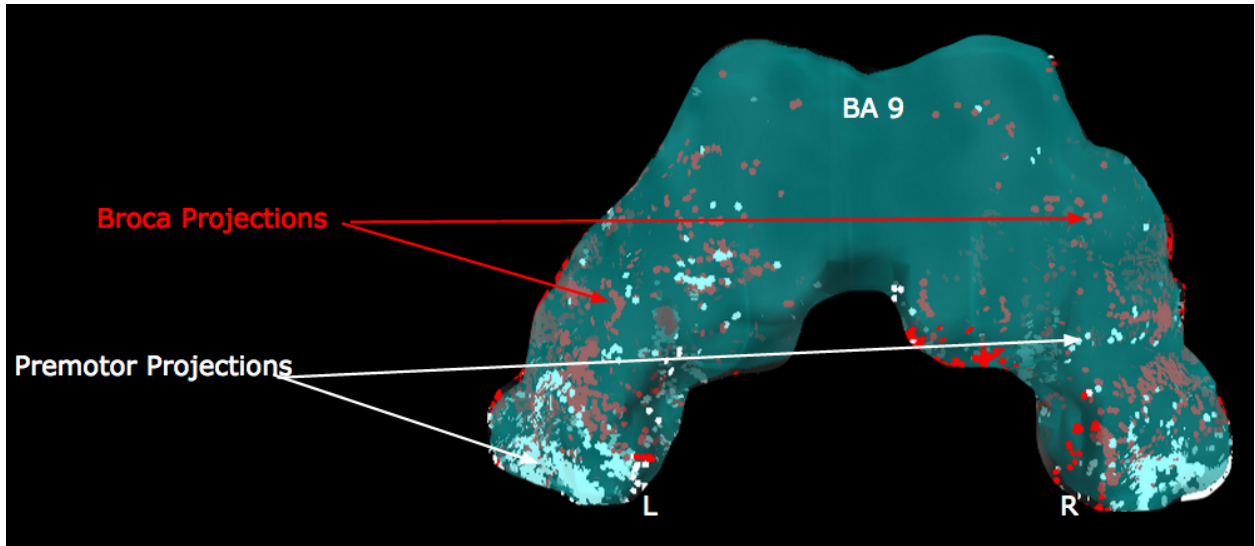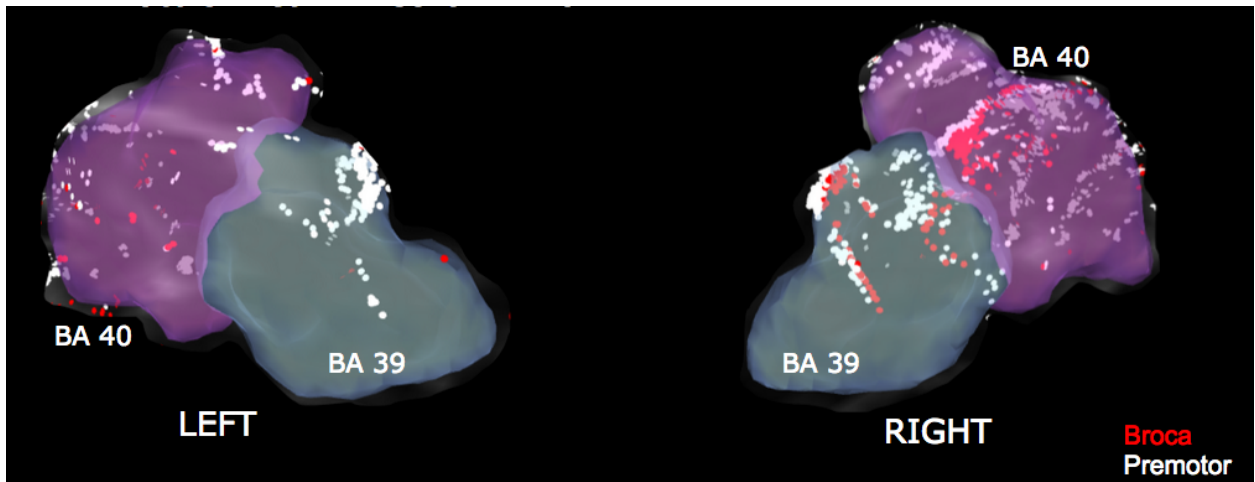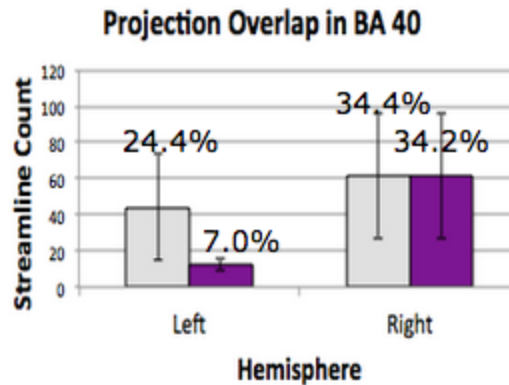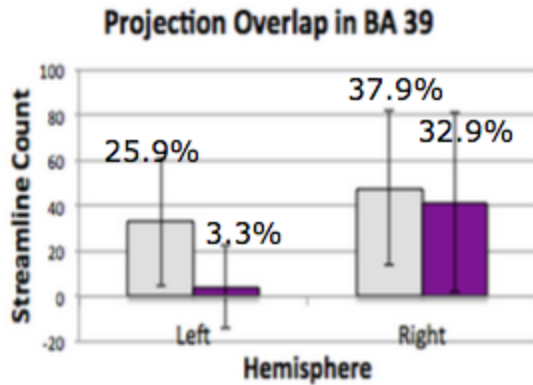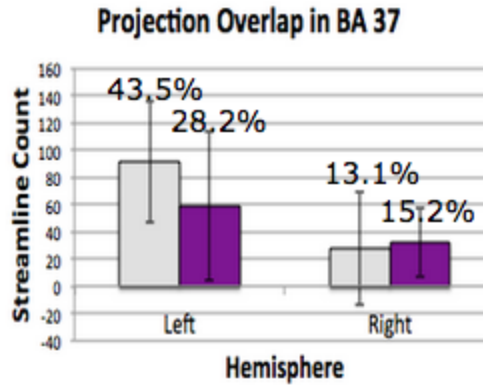
Figure 6: Example of Region Projecting Tendency

Figure 7: Example of Region Interactions

Charts

Chart 1: Regions of Overlap
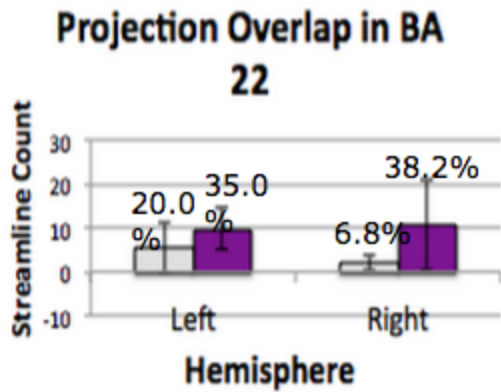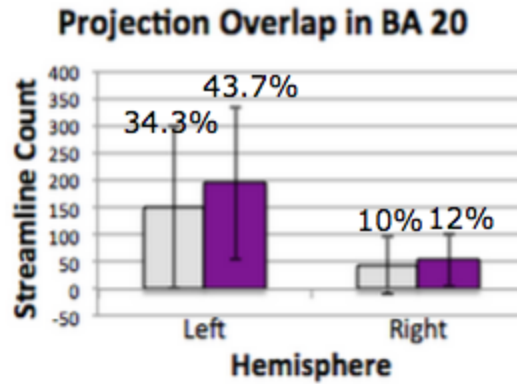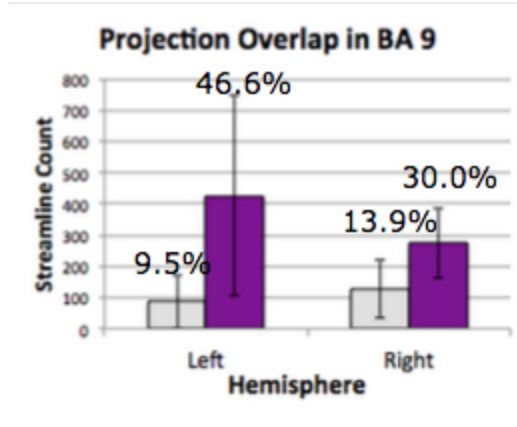
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