Extended Broca's Area in the Connectome of Language in Adults: Subcortical Single-Subject Analysis Using DTI Tractography.

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SUPPLEMENTARY MATERIAL

Body text: 457 words; Figures: 2; Tables: 3

Rationale for the description and analysis of WM fascicles

The metrics (i.e., number of lines and length) used to quantify the fascicles (Supplementary Table 1) were analyzed specifically for the interpretation of the results.

Fascicles were generated using real-time tracing of WM fibers in diffusion tensor imaging (DTI) data. An expert-based approach, which joined anatomical and clinical knowledge, was used to attribute fibers to a specific fascicle, relying on 3-dimensional anatomic knowledge.

Each fascicle was generated by the addition of lines figuring the result of tracing (stopping mode > 0.25; threshold of tracing curvature ≥ 0.7 degree/mm). The tracing was initiated in a cubic seeder (volume of interest) which had a 2.5-mm edge. Tracing began with several seed points separated by 1 mm (grid spacing = 1 mm), and up to 27 lines could be generated by one cubic seeder. To simplify the anatomic analysis, a line was displayed as a tube to resemble the macroscopic organization of brain WM fibers; we will refer to these lines as fibers. The number of lines depended on three parameters, which were visually adjusted: the addition of seeders to generate the fascicle, the overlapping of seeders, and the decision to stop the addition of a new seeder. We minimized the overlapping of seeders to keep the density of fibers homogeneous within the fascicle. Seeders were moved slightly to reduce overlap without loss of fibers belonging to the fascicle. On average, one fascicle was generated from 5.1 ± 2.5 seeders. The decision to add a new seeder was balanced by the need to minimize overlapping and the need to search for new fibers. Seeding was stopped when the on-line visualization of fibers produced new fibers obviously not included in the fascicle (e.g., presence of a fronto-parietal fiber when tracing the arcuate fascicle). For each fascicle, the number of lines was considered to be sufficient to evaluate, the relative differences between hemispheres or subjects.

The length of the fascicles was quantified by using the average value of points (number of points/number of lines). Length was used to evaluate the reliability of the methodology, based on the hypothesis that the length of the fascicle would be similar within the right and left hemispheres (Supplementary Fig 1). This was established for all of the fascicles (null hypothesis not rejected; type I error set to 0.005 after Bonferonni correction). The differences in shape and density of the fibers for the different fascicles (anatomical considerations) did not permit comparison according to the average length. An analysis of ratios (i.e., number of lines/number of seeders) was also used to evaluate the reproducibility of the method (Supplementary Fig 2). Reproducibility was confirmed, since we did not find any difference between ratio values for the right and left hemispheres.

<u>Supplementary Figure 1</u>. Evaluation of the reproducibility of fascicle generation (language study) – Part I: Average line length

Average length of lines (number of points/number of lines; mean value, SD; n = 12 subjects; logarithmic y-axis) for each fascicle (same color code and abbreviations used in the manuscript) within the left (white bar) and right (black bar) hemispheres. The p values of t-tests testing the null hypothesis (one-tailed † and two-tailed) of the difference between right and left hemisphere are given at the bottom.

<u>Supplementary Figure 2.</u> Evaluation of the reproducibility of fascicle generation (language study) – Part II : Ratio lines over seeders

Ratio lines over seeders (mean value, SD; n = 12 subjects) for each fascicle (same color code and abbreviations used in the manuscript) within the left (white bar) and right (black bar) hemispheres. The manual placement of seeders (n=1174) was done blind of the calculation of this ratio. The p values of t-tests testing the null hypothesis (one-tailed † and two-tailed) of the difference between right and left hemisphere are given at the bottom.

Supplementary Table 1. Descriptive parameters of fascicles

Number of lines (n) and length (number of points over n; arbitrary unit, a.u.) of the 10 fascicles (see text for abbreviations) systematically identified within the right (RH) and left (LH) hemisphere in 12 subjects. (Index of laterality = LH-RH / LH+RH).

		lines (n) length (a.u.)								index of laterality (+ leftward. - rightward)	
system	fascicle	RH				LH					
		system		fascicle		system		fascicle		system	fascicle
		mean	sd	mean	sd	mean	sd	mean	sd		
inferior	UF			53.92	31.11			40.08	17.44		-0.12
				119.55	17.52			102.51	14.35		-0.08
	TOF			105.17	40.26			105.33	41.61		0.00
		343.67	55.61	141.31	19.90	336.83	84.93	144.53	20.25	-0.02	0.01
	IFTOF	631.83	208.07	119.00	35.82	678.14	56.85	104.92	28.46	0.08	-0.06
				207.29	41.18			208.26	26.09		0.01
F3	IFOF			65.58	18.22			86.50	33.79		0.12
				218.53	41.24			222.84	24.68		0.02
	TrOrS			187.08	58.58			184.00	44.87		0.00
		327.33	68.01	90.69	13.17	292.58	65.87	95.30	15.74	-0.06	0.02
	OpPMF	173.86	16.18	140.25	36.65	169.25	20.28	108.58	39.86	-0.01	-0.14
				83.17	7.72			73.94	9.48		-0.06
superior	AF			97.17	51.84			166.92	43.06		0.29
				280.88	408.52			177.35	17.88		-0.02
	fpSLF	341.58	46.10	136.33	28.95	370.50	71.40	90.92	23.86	0.03	-0.20
		509.10	411.51	130.26	15.05	408.05	30.73	124.59	20.44	-0.03	-0.03
	sPTS			108.08	20.47			112.67	51.93		-0.02
				97.96	12.64			106.10	15.56		0.04
TrSMA					76.83	12.09				n.a.	
					171.55	31.47					
sum (but TrSMA)			1012.58	99.95			999.92	165.74			-0.01
			1314.79	482.52			1255.43	83.11			0.00

Supplementary Table 2. Connections of the arcuate fascicle and of the fronto-parietal branch of the superior longitudinal fascicle.

Number of connections within the left (LH) and right (RH) hemisphere (12 subjects) according to cortical territories (rostral, within the frontal lobe, and caudal within the parieto-temporal region), for the arcuate fascicle (AF) and the fronto-parietal branch of the superior longitudinal fascicle (fpSLF).

	connection	AF			fpSLF		
		RH	LH	total	RH	LH	total
rostral	premotor cortex	9	11	20	12	12	24
	pars opercularis	5	11	16	5	4	9
	pars triangularis	1	1	2	0	0	0
caudal	middle temporal gyrus	11	12	23	0	0	0
	Wernicke's area	0	4	4	0	0	0
	Geschwind's area	0	0	0	12	12	24
	total	26	39	65	29	28	57

Supplementary Table 3. Occurrence of the variable bundles linked with Broca's area

Occurrence (number of identifications) of the variable bundles linked with Broca's area (see text for abbreviations) within the right (RH) and left (LH) hemispheres (12 subjects). (Index of laterality = LH-RH / LH+RH).

variable bundles		occurrence				index of laterality	
group	bundle	RH		LH		+ leftward - rightward	
		group	bundle	group	bundle	group	bundle
frontal	OpPM-SMA	13	6	8	2	-0.24	-0.50
	TrOr-SMA		6		3		-0.33
	TrOrS-Prefrontal		0		2		1.00
	TrOrS-frontopolar		1		1		0.00
ventral	TrOrS-Wernicke ventral	8	0	8	1	0.00	1.00
	TrOrS-T2 ventral		4		4		0.00
	TrOrS-Geschwing ventral		4		3		-0.14
dorsal	TrOrS-Wernicke dorsal	3	0	6	1	0.33	1.00
	TrOrS-T2 dorsal		0		1		1.00
	TrOrS-Geschwind dorsal		3		4		0.14
distal	TrORs-Psup/PO	5		10		0.33	
	total	29		32		0.05	