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# Anatomo-functional correspondence in the voice-selective regions of human prefrontal cortex

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## Abstract

Group level analyses of functional regions involved in voice perception show evidence of 3 sets of bilateral voice-sensitive activations in the human prefrontal cortex, named the anterior, middle and posterior Frontal Voice Areas (FVAs). However, the relationship with the underlying sulcal anatomy, highly variable in this region, is still unknown. We examined the inter-individual variability of the FVAs in conjunction with the sulcal anatomy. To do so, anatomical and functional MRI scans from 74 subjects were analyzed to generate individual contrast maps of the FVAs and relate them to each subject's manually labeled prefrontal sulci. We report two major results. First, the frontal activations for the voice are significantly associated with the sulcal anatomy. Second, this correspondence with the sulcal anatomy at the individual level is a better predictor than coordinates in the MNI space. These findings offer new perspectives for the understanding of anatomical-functional correspondences in this complex cortical region. They also shed light on the importance of considering individual-specific variations in subject's anatomy.

**Keywords:** Human, fMRI, Voice perception, Individual variability, Sulcal anatomy

## 30 1. Introduction

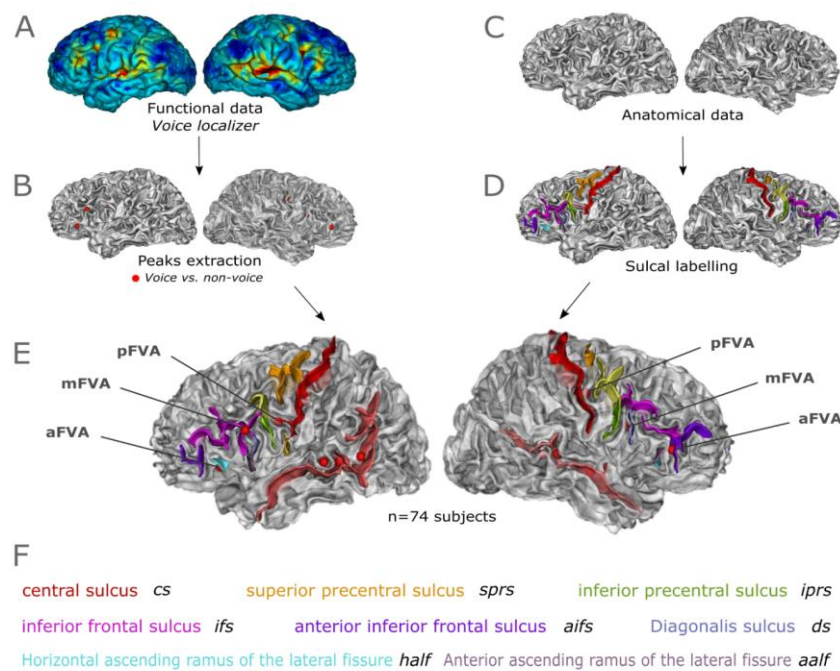
31 The cerebral processing of voice information has been shown to involve several  
32 voice-selective cortical regions: the Temporal Voice Areas of bilateral secondary  
33 auditory cortex (Belin et al., 2000; Pernet et al., 2015) but also 3 bilateral regions  
34 of frontal cortex we called the Frontal Voice Areas (FVA; Aglieri et al., 2018). Based  
35 on group-averaged fMRI results, the anterior frontal voice area (aFVA) in the left  
36 hemisphere appears to correspond to the *pars orbitalis* of the inferior frontal gyrus  
37 (IFG) (Brodmann area BA 47) and in the right hemisphere to the *pars triangularis* of  
38 the IFG (BA 45); the middle frontal voice areas (mFVA) bilaterally correspond to the  
39 upper part of the *pars opercularis* of the IFG (BA 44); and the posterior frontal voice  
40 areas (pFVAs) to the precentral gyrus close to the junction with the middle frontal  
41 gyrus (BA 6). However, the localization of the FVAs seems much more variable at  
42 the individual participant level.

43 A portion of the inter-individual variability in the occurrence and position of the FVAs  
44 could conceivably be related to the high inter-individual variability in the anatomy  
45 of prefrontal folding patterns. Detailed examination of prefrontal sulci such as the  
46 horizontal ascending ramus of the lateral fissure (Sprung-Much and Petrides,  
47 2020), the ascending ramus of the lateral fissure or the diagonalis sulcus (Sprung-  
48 Much and Petrides, 2018), has uncovered strong variability in their existence and  
49 spatial organization. Indeed, correspondence between the localization of functional  
50 activations and local sulcal anatomy has been observed in multiple cases, such as  
51 for the position of the motor hand representation relative to the 'hand knob' of  
52 Central Sulcus (Sun et al., 2012), the relationship between cortical folding in the  
53 visual cortex and retinotopic maps (Rajimehr and Tootell, 2009), or the localization  
54 of the temporal voice areas relative to the 'Superior Temporal Asymmetrical Pit' of  
55 the Superior Temporal Sulcus (Bodin et al., 2018). One can also mention some  
56 anatomo-functional correspondances at the level of the lateral prefrontal cortex  
57 (Amiez et al., 2016, 2006; Amiez and Petrides, 2018; Zlatkina et al., 2016), the  
58 cingulate (Amiez et al., 2013; Amiez and Petrides, 2014), the orbitofrontal cortex  
59 (Li et al., 2015), the visual cortex (Benson et al., 2014, 2012; Weiner et al., 2018,  
60 2014; Witthoft et al., 2014), as well as the lateral parietal cortex (Konen and  
61 Kastner, 2008; Tootell et al., 1997). We can also highlight a study (Lopez-Persem

62 et al., 2019) that showed that the sulcal organization is a better predictor than MNI  
 63 coordinates to identify the functional organization of the ventromedial prefrontal  
 64 cortex.

65 Here we address that question by examining at the individual subject-level the  
 66 relative location of the FVAs and frontal sulci using anatomical and functional MRI  
 67 data from 74 healthy adult participants (Figure 1). We assess (1) whether FVAs show  
 68 consistent relationship to particular frontal sulci; and (2) whether these  
 69 relationships could be more predictive of the location of a particular FVA than the  
 70 group-average MNI coordinates.

71 We observe consistent associations between the FVAs and specific sulci. For the  
 72 mFVAs and pFVAs, the distance to the associated sulcus is ~2-3 times shorter than  
 73 the distance to the average MNI coordinate of that FVA.



74

75 **Figure 1: Summary of the methodology used to examine anatomo-functional**  
 76 **correspondences between FVAs and frontal sulci at the individual level.**

77 *A. The functional map of the contrast Vocal sounds vs. Nonvocal sounds from the Voice Localizer is shown overlaid on the 3D*  
 78 *cortical anatomy in one participant. B. Local voice selectivity maxima, individually extracted in search zones*  
 79 *around the group-average locations of the FVAs, are represented as red spheres centered on each local*  
 80 *maximum C. 3D mesh of the gray-white matter interface. D. Prefrontal sulci of interest were individually*  
 81 *labeled. E. Anatomical and functional data are registered for computing the distance between sphere centers*  
 82 *and sulci. F. Frontal sulcus nomenclature used and associated color code: Central sulcus (cs), superior precentral*  
 83 *sulcus (sprs), inferior precentral sulcus (iprs), inferior frontal sulcus (ifs), anterior inferior frontal sulcus (aifs),*  
 84 *anterior ascending ramus of the lateral fissure (aalf), horizontal ascending ramus of the lateral fissure (half),*  
 85 *diagonalis sulcus (ds).*

## 86 2. Materials and methods

### 87 2.1 Participants

88 We scanned seventy-four ( $n = 74$ ; 36 males and 38 females ; age (mean  $\pm$  SD) =  
89  $38,5 \pm 19,7$ ) healthy adult volunteers on the localizer scan as part of experiments  
90 of the Voice Neurocognition Laboratory of the Institute of Neuroscience and  
91 Psychology at University of Glasgow. Participants were recruited from the  
92 population of Glasgow and were of various ethnic backgrounds, education and  
93 manual lateralization. Participants all provided written informed consent prior to  
94 participation, in accordance with the Declaration of Helsinki. The experiments were  
95 approved by the local ethics committee at University of Glasgow.

### 96 2.2 Voice localizer protocol and stimuli

97 The voice localizer consists of a ten minutes and twenty seconds-long block design  
98 with 40 eight seconds-long blocks of either vocal (20 blocks) or non-vocal (20  
99 blocks) sounds from stimuli already used in Belin et al., 2000. Stimuli were  
100 presented using Media Control Functions (DigiVox, Montreal, Canada) via  
101 electrostatic headphones (NordicNeuroLab, Norway; or Sensimetrics, USA) at a  
102 comfortable level (80–85 dB SPL). The forty blocks are intermixed with twenty  
103 periods of silence allowing the hemodynamic to relax. Blocks consisted of a mixture  
104 of either vocal sounds or non-vocal sounds, with at most a 400 ms delay between  
105 consecutive stimuli. The order of blocks was attributed randomly and was similar  
106 for all participants. Vocal blocks contained only sounds of human vocal origin  
107 (excluding sounds without vocal fold vibration such as whistling or whispering)  
108 obtained from 47 speakers (7 babies, 12 adults, 23 children and 5 elderly people)  
109 and consisted of speech sounds (words, syllables or sentence extracts in different  
110 languages) and non-speech vocal sounds (emotional positive or negative sounds  
111 like laughs, sighs, or cries, and neutral sounds like coughs, and onomatopoeias).  
112 Non-vocal blocks consisted of natural sounds (from natural sources like falls, sea  
113 waves, wind, and from various animals like cats, dogs, lions, and elephants) and of  
114 man-made sources (from objects like cars, glass, alarms, and clocks, and from

115 (classical) musical pieces). Stimuli (16 bit, mono, 22,050 Hz sampling rate) were  
116 normalized for RMS (same normalization for all stimuli); a 1-kHz tone of similar  
117 energy is provided for calibration. Stimuli are available for download at:  
118 <https://amubox.univ-amu.fr/s/edQWc7oSiaRNYsP>.

## 119 2.3 MRI acquisitions

120 All scans were acquired on a 3T Siemens (Erlangen, Germany) Tim Trio scanner at  
121 the Centre for Cognitive Neuroimaging University of Glasgow. All fMRI data were  
122 acquired using a single-shot gradient-echo echo-planar imaging (EPI) sequence  
123 with the following parameters: field of view (FOV) = 210 × 210 mm<sup>2</sup>, 32 slices per  
124 volume, interleaved slices order, voxel size 3 × 3 × 3.3 mm<sup>3</sup>, acquisition matrix 70  
125 × 70, flip angle = 77°, echo time (TE) = 30 ms. The repetition time (TR) was 2 s with  
126 an acquisition time (TA) of 2 seconds resulting in quasi-continuous scanning noise  
127 Participants were scanned while passively listening to the stimuli and keeping their  
128 eyes closed. For each participant, 310 EPI volumes were acquired together with a  
129 high-resolution 3D T1-weighted sagittal scan (voxel size 1mm<sup>3</sup> isotropic; acquisition  
130 matrix 256 256 192).

## 131 2.4 Preprocessing of anatomical data

132 T1w MRIs were processed using the Morphologist pipeline implemented in Brainvisa  
133 (Brainvisa 5.0.2 singularity version). This pipeline performed automatically T1 bias  
134 corrections, sulcus extraction and mesh generation. We then manually labeled the  
135 sulci of interest in the vicinity of the FVAs. We used the manual tool 'Anatomist  
136 show descriptive model' and the default nomenclature from Brainvisa, with  
137 modification of selected sulcus names to adopt the nomenclature of the Petrides  
138 atlas (Petrides, 2016). We labeled the central sulcus (cs), superior/inferior  
139 precentral sulcus (sprs/iprs), inferior frontal sulcus (ifs), diagonalis sulcus (ds),  
140 horizontal ascending ramus of the lateral fissure (half), anterior ascending ramus  
141 of the lateral fissure (aalf) and anterior inferior frontal sulcus (aifs - generated by  
142 brainvisa but in our study it might correspond to the sulci pretriangular sulcus (prts)  
143 combined with some other highly variable sulci in the petrides atlas). The labeling  
144 was performed in all 74 participants, with n=9 participants initially labeled

145 independently by 2 experimenters. The two experimenters are disagreed about the  
146 labeling of any sulcus only 5 times across the 9 participants (disagreed about one  
147 labeling of the aalf, 2 times about the ds, 1 times about the sprs and 1 time about  
148 the iprs); they are agreed (or disagreed with only one or two branch on the sulcus)  
149 in all the other cases i.e. 96% of the cases. This analysis confirmed the reliability of  
150 the labeling of the frontal sulcus for the 74 participants.

## 151 2.5 Preprocessing of functional data

152 SPM VERSION was used to preprocess functional data. We made a realignment of  
153 the 310 EPI volumes, T1w native image have been then coregistered to the mean  
154 of realigned EPIs through normalized mutual information, smoothing (6x6x6) of the  
155 mean of realigned EPIs, and T1 images were segmented into their native space  
156 tissue components (gray and white matter, and CSF). Next we computed an fMRI  
157 model estimation with the multiple conditions (names = VOCAL and NONVOCAL;  
158 duration = 8 and 8; onset = VOCAL [22 62 82 112 132 162 202 222 242 262 312  
159 352 372 402 432 462 482 512 542 572], NONVOCAL[12 32 52 102 122 142 182 232  
160 282 302 322 342 382 422 442 472 502 522 552 592]) and motion parameters  
161 determined during preprocessing as regressors of no interest. We then calculated  
162 for each individual subject its contrast map corresponding to the beta maps for  
163 VOCAL minus the beta map for NON-VOCAL. Voice-selective regions were  
164 identified as those showing a significantly greater activity for voice than for non-  
165 voice categories for each individual participant ( $p$ value < 0,001 uncorrected).

## 166 2.6 Definition of the search zone at the individual level

167 Six Frontal Voice Areas have been described by Aglieri et al., 2018 in prefrontal  
168 cortex based on the average activation maps from 90 DARTEL-registered  
169 participants. The coordinates in the MNI space of the average peaks are : aFVA left  
170 (-39 27 -3) and aFVA right (54 32 0) approximately corresponding to the location  
171 of the pars orbitalis/triangularis of the Inferior Frontal Gyrus, mFVA left (-48 16 21)  
172 and mFVA right (48 18 24) corresponding to the pars opercularis of the Inferior  
173 Frontal Gyrus , pFVA left (-52 -8 48) and pFVA right (51 -2 48) corresponding to the  
174 Precentral Gyrus. We choose to use these 6 average peaks to guide the

175 identification of the functional local maxima in each individual's native space. We  
176 considered those three locations in each hemisphere as the center of a limited  
177 search zone and we selected the peak of the voice vs. non-voice contrast in these  
178 regions – if one could be found. Two experimenters independently extracted  
179 individual FVAs in a sample of 15 participants to examine inter-rater agreement and  
180 refine the search strategy. The two experimenters agreed on the (x,y,z) coordinates  
181 and the nomenclature (anterior, middle or posterior FVA) in 52,2% of the cases  
182 (47/90 peaks); agreed on the (x,y,z) coordinates but not for the nomenclature in  
183 36,7% of the cases (33/90 peaks); and disagreed with the coordinates in 11,1% of  
184 the case (10/90 peaks) with a mean difference (in mm) between the coordinates of  
185 (7, 19, 16). We made a second round of evaluation after corrections and we  
186 obtained 100% of agreement between coordinates and nomenclature for the two  
187 experimenters.

## 188 **2.7 Co-registration functional on anatomical data**

189 The coregistration between anatomy and function has been computed with  
190 Brainvisa. The referentials of both objects were placed in the same space (native  
191 anatomy) in order to visualize the spheres on the individual mesh of each subject.  
192 The aim of the sphere generation is to visually highlight local functional maxima  
193 and to describe the anatomical localization of them based on sulcal anatomy. These  
194 functional activations were also transformed in MNI space to determine the global  
195 localisation of the FVAs' cloud of points and to compare the accuracy of  
196 measurements in MNI space considering or not the sulcal anatomy.

## 197 **2.8 Distance measurement between functional activations and** 198 **the nearest sulci**

199 To assess the anatomo-functional relationship between functional peaks and sulci,  
200 we performed distance measurements between the 8 frontal sulci of interest  
201 (central sulcus, superior-inferior precentral sulcus, inferior frontal sulcus, diagonalis  
202 sulcus, horizontal ascending ramus of the lateral fissure, anterior ascending ramus  
203 of the lateral fissure and anterior inferior frontal sulcus) and all the individual FVAs.



204 We manipulated the Brainvisa objects (functional spheres, meshes and sulci) using  
205 the Brainvisa 5.0.2 singularity version, and we performed an Euclidian distance  
206 estimation with Spicy (numpy/python).

## 207 3. Results

### 208 3.1. Individual occurrence of the Frontal Voice Areas

209 We first examined the occurrence at the individual level of the different FVAs in our  
210 sample of 74 participants. We report in Table 1 the proportion of participants in  
211 whom each of the FVAs could be observed or not, individually in the left and/or  
212 right hemispheres. The most commonly observed FVA was the pFVA that could be  
213 identified bilaterally in 37,9% of the sample. The anterior FVA was much less  
214 frequently observed, with an absence around 80% in the sample of 74 participants.  
215 Binomial tests conducted for each of the three FVAs confirmed that the distribution  
216 is statistically different from chance in the aFVAs, with many more participants in  
217 whom none could be found, and much fewer participants in whom it could be  
218 identified at all, than the expected 25%. The number of bilateral pFVAs was also  
219 significantly higher than the 25% proportion expected by chance.

%	Left	Right	Bilateral	none
<b>aFVA</b>	9 (12,2%)*	4 (5,4%)**	2 (2,7%)**	59 (79,7%)**
<b>mFVA</b>	11 (14,9%)	19 (25,7%)	24 (32,4%)	20 (27,0%)
<b>pFVA</b>	12 (16,2%)	12 (16,2%)	28 (37,9%)*	22 (29,7%)

220 **Table 1: Individual occurrence of the FVAs.**

221 *Each cell indicates, for each of the 3FVAs (rows), the number (and proportion) of participants in whom the*  
222 *FVA was identified in a single hemisphere (left or right), in both hemispheres (bilateral) or in none. Binomial*  
223 *tests with Bonferroni correction ( $\alpha/3$ ) were performed to identify deviations from chance distribution across*  
224 *the 4 cells. \*:  $p < 0,05$  corr.; \*\*:  $pvalue < 0,001$  corr.*

### 225 3.2 Individual occurrence of the frontal sulci

226 In parallel we manually labeled and examined the individual occurrence of the main  
227 frontal sulci located around the FVAs. Table 2 indicates the proportion of  
228 participants in whom each of the main frontal sulci of interest were observed.  
229 Variability in occurrence concerned mostly the diagonalis sulcus (ds), the horizontal

230 ascending ramus of the lateral fissure (half) and the anterior ascending ramus of  
 231 the lateral fissure (aalf), which were absent in several participants.

<b>Sulci</b>	<b>Left</b>	<b>Right</b>
<b>Horizontal ascending ramus of the lateral fissure</b>	90,5%	91,9%
<b>Anterior ascending ramus of the lateral fissure</b>	94,6%	97,3%
<b>Diagonalis sulcus</b>	62,2%	55,4%
<b>Central sulcus</b>	100%	100%
<b>Inferior frontal sulcus</b>	100%	100%
<b>Anterior inferior frontal sulcus</b>	100%	100%
<b>Inferior precentral sulcus</b>	100%	100%
<b>Superior precentral sulcus</b>	100%	100%

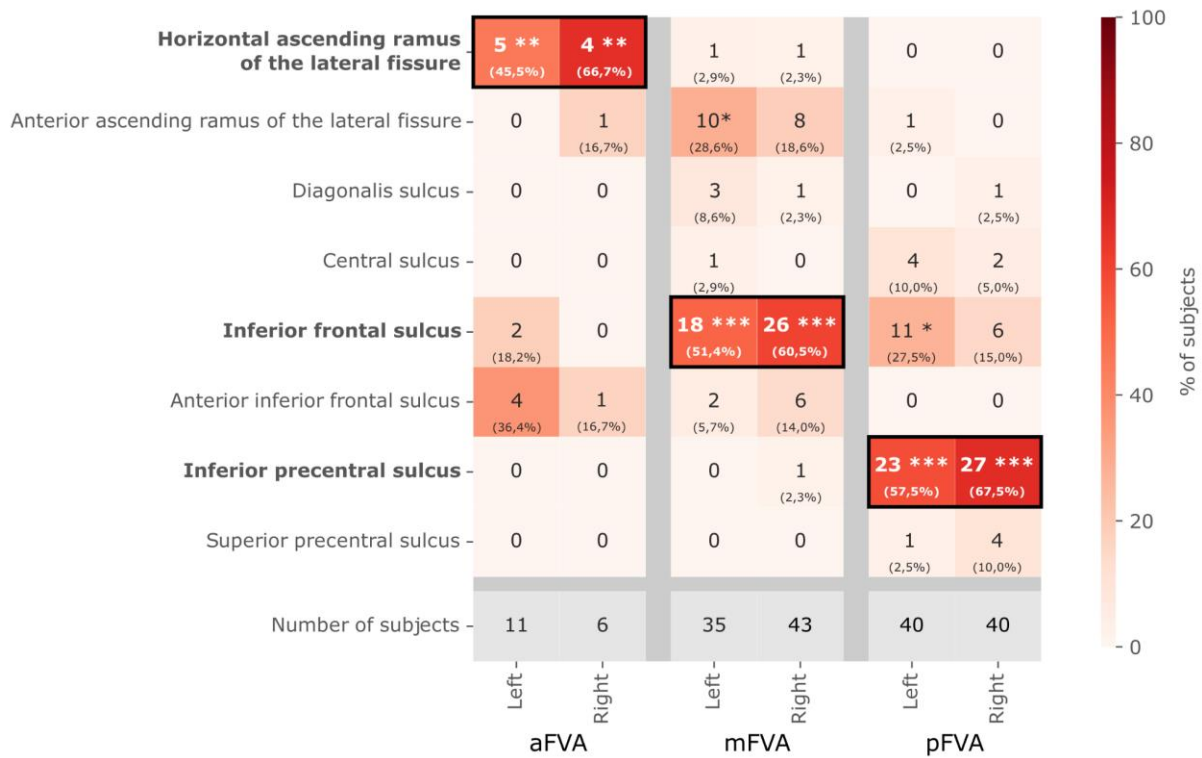
232 **Table 2: Individual occurrence of the main prefrontal sulci**

233 *Cells indicate, for each sulcus of interest, the proportion of participants in which the sulcus is present in the left*  
 234 *and right hemispheres.*

### 235 3.3 Relationship between the FVAs and frontal sulci

236 Next, we assessed whether each FVA was located closer to a particular prefrontal  
 237 sulcus than the others. Figure 2 indicates, for each of the 6 FVAs, the proportion of  
 238 participants in whom the FVA was found closer to each of the main sulci of interest,  
 239 in the individual (native) space. We found strong, symmetrical associations  
 240 between each FVA and a particular sulcus. Bonferroni-corrected binomial tests  
 241 confirmed that there were greater-than-chance associations between each FVA  
 242 and a particular sulcus, symmetrically across hemispheres: the left and right aFVAs  
 243 were significantly associated with the horizontal ascending ramus of the lateral  
 244 fissure (half); the left and right mFVAs were most often closest to the inferior frontal

245 sulcus (*ifs*) ; the left and right pFVAs were most often closest to the inferior  
 246 precentral sulcus (*iprs*) (Fig 2).



247

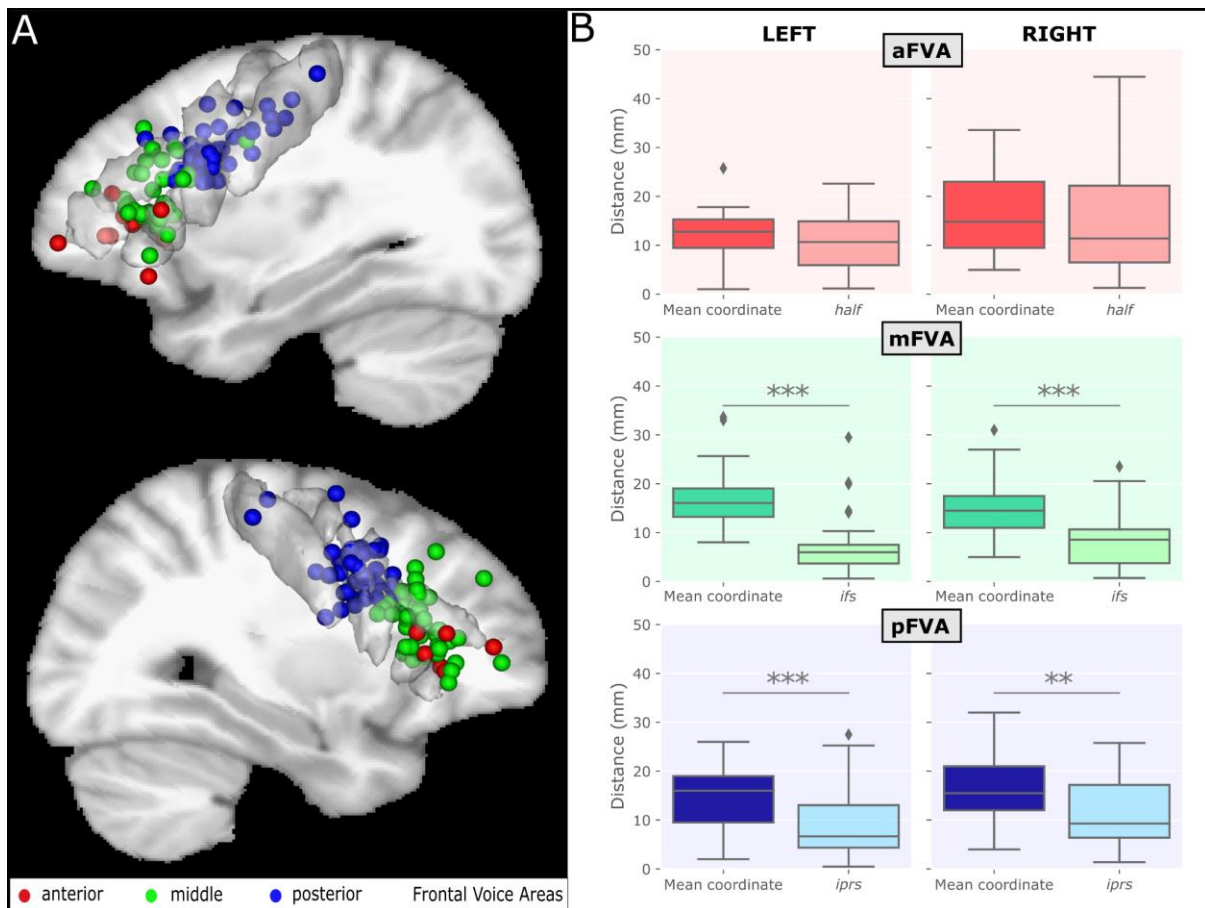
248 **Figure 2: Association of FVAs with particular sulci**

249 For each FVA (columns), cells indicate the number (and proportion) of participants in whom the FVA peak was  
 250 closer to each sulcus of interest (rows). Stars indicate cells for which the proportion of participants is  
 251 significantly above the 12.5% expected by chance as assessed by a Bonferroni-corrected Binomial test. \*:  $p < 0,05$   
 252 corr.; \*\*:  $p < 10^{-7}$  corr.; \*\*\*:  $p < 10^{-12}$  corr. The bottom row in gray indicates the number of participants in whom  
 253 each FVA was observed.

### 254 3.4 Distance to sulcus vs. distance to average coordinate in the 255 MNI space

256 Finally, we assessed whether the distance to the associated sulcus in the individual  
 257 space was more predictive of each FVA localization than its distance to the average  
 258 coordinate computed across individuals in the MNI space. Indeed, the location of  
 259 FVAs was highly variable across individuals, resulting in widely spread peaks in MNI  
 260 space (Fig 3a). Figure 3b shows, for each of the 6 FVAs, the distribution of distances  
 261 to average MNI coordinate vs. the distance to associated sulcus, after  
 262 transformation to MNI space, for normalization. For the aFVAs, median distances  
 263 were smaller relative to the *half* sulcus than to the average MNI coordinates, but

264 not significantly (aFVA left pvalue=0,49; aFVA right pvalue=0,31). For the middle  
 265 and posterior FVAs, the difference was stronger, and highly significant in both  
 266 hemispheres (mFVA left pvalue=5,9.10<sup>-7</sup>; mFVA right pvalue=2,8.10<sup>-8</sup>; pFVA left  
 267 pvalue=8,2.10<sup>-8</sup>; pFVA right pvalue=6,1.10<sup>-8</sup>). Non-parametric Wilcoxon tests were  
 268 performed to compare two-by-two the medians and Bonferroni correction ( $\alpha/3$ )  
 269 was applied. Median distances to MNI average are reported in table3.



270

271 **Figure 3: FVA spatial dispersion in functional vs. anatomical space**

272 A. Dispersion of FVAs peaks from every individual are shown in MNI space. aFVAs are represented in red,  
 273 mFVAs in green and pFVAs in blue.

274 B. For each FVA, we show the distribution of the distances to the MNI average (left) vs. the distances to the  
 275 associated sulcus from the same individual. Stars indicate significance of the difference as assessed by  
 276 Wilcoxon's after Bonferroni correction: \*:pvalue<0,05corr.; \*\*:pvalue<0,01corr.; \*\*\*:pvalue<0,001corr.

277

	LEFT		RIGHT	
	Median distance to mean coordinate	Median distance to sulcus	Median distance to mean coordinate	Median distance to sulcus
aFVA	11,0	8,6	10,6	4,4
mFVA	14,0	5,6	12,2	4,8
pFVA	12,9	2,9	11,4	4,2

278 **Table 3: Median distances to MNI average**

279 *Cells indicate, for each boxplot represented in the fig.3, the median of distances between individual peaks and*  
280 *either group-level average or corresponding sulcus.*

## 281 4. Discussion

282 We show here that there is a clear relationship between the functional localization  
283 of the Frontal Voice Areas and the sulcal anatomy of prefrontal sulci at the  
284 individual level. We also show that this sulcal anatomy can be more informative of  
285 an individual's FVA localization than average coordinates from group-level analysis.

### 286 4.1 Individual analysis reveals high inter-subject variability in 287 both functional location of the FVAs and precise sulcal anatomy

288 In many participants we were able to identify at the individual level the FVAs  
289 previously described at the group level (Aglieri et al., 2018) (Table 1). This was  
290 particularly the case for the mFVA and pFVA that could be observed in at least one  
291 hemisphere in nearly three quarters of the participants, and in both hemispheres  
292 in about a third of the participants. The aFVA was much less frequently observed,  
293 however, seen in either hemisphere in only 1 subject out of 5 (Table 1). There was  
294 no clear hemispheric lateralization in this pattern, mirroring the bilateral and  
295 essentially symmetrical group-level FVAs. When observed, individual-level FVAs  
296 were also fairly variable in their localization, as shown in Fig. 3a.

297 Individual examination of sulcal anatomy in the inferior prefrontal region also  
298 revealed high variability, both in the shape of the sulci, as well as in the presence  
299 of some classical sulci (Table 2). The diagonalis sulcus, in particular, could be  
300 identified in a little more than half the participants, in line with previous studies.

### 301 4.2 Individual analysis reveals a relationship between the Frontal 302 Voice Areas and prefrontal sulcal anatomy

303 Despite functional and anatomical variability, we observed a clear correspondence  
304 between anatomy and function. When they could be observed in either hemisphere,  
305 the aFVAs were found most often closest to the horizontal ascending ramus of the  
306 lateral fissure; the mFVAs closest to the inferior frontal sulcus; and the pFVAs  
307 closest to the inferior precentral sulcus.

308 Structure-function relationships have already been reported in the literature, for  
309 example the position of the motor hand representation relative to the 'hand knob'  
310 of Central Sulcus (Sun et al., 2012), or the localization of the temporal voice areas  
311 relative to the 'Superior Temporal Asymmetrical Pit' of the Superior Temporal  
312 Sulcus (Bodin et al., 2018). Other examples include K.Weiner's work on the  
313 functional implications around the fusiform gyrus (Weiner and Zilles, 2016), or  
314 Arcaco's buried gyral folds along the superior temporal sulcus in macaque lateral  
315 temporal cortex, which selectively predict the location of face-sensitive regions  
316 (Arcaro et al., 2020). Finally, we can mention the work of C. Amiez and M. Petrides  
317 on structure-function relations, such as the conditional visuomotor activity of the  
318 hand and the frontal eye field which are located in the superior precentral sulcus  
319 (Amiez et al., 2006). Our findings are consistent with these previous studies, and  
320 extend the notion of relationships between anatomy and function to the prefrontal  
321 cortex.

### 322 4.3 Individual anatomy can be more predictive of functional 323 location than group-level average coordinates

324 We found that for the middle and posterior FVAs in both hemispheres, the distance  
325 between the functional peak and the associated sulcus was on average  
326 considerably smaller than its distance to the group-level average coordinate. The  
327 median distance between the mFVA and the inferior frontal sulcus was around 2  
328 times smaller than to group-level mFVA average; median distance to inferior  
329 precentral sulcus was about 3 times smaller than to group average for the pFVAs  
330 (Figure 3, Table 3).

331 In contrast, for the most anterior FVAs, we did not find a significant difference  
332 between distance to the average coordinate and to the horizontal ascending ramus  
333 of the lateral fissure (*half*). Possible explanations for this could be: (1) lack of  
334 statistical power due to fact that individual aFVAs could only be observed in a very  
335 small number of participants (11 participants showed this activation in the left  
336 hemisphere and 6 in the right hemisphere); (2) the *half* is a highly variable sulcus  
337 that was often absent. Better characterizing the complexity of the sulcal



338 morphology of this region is crucial for understanding the role of functional  
339 activations in language-related studies (Sprung-Much and Petrides, 2020).

340 Thus, part of the functional variability observed in FVA localization seems to be  
341 explained by sulcal variability, and for the m and pFVAs, individual anatomical  
342 sulcation seems a better indicator of function localization than the barycenter of a  
343 rather spread out point cloud. This observation is in line with previous studies such  
344 as (Rivière et al., 2022) and (Coalson et al., 2018) that showed that spatial  
345 normalization is not optimal for dealing with inter-subject variability in cortical  
346 morphology.

#### 347 4.4 Functional roles of the three FVAs based on sulcal anatomy

348 Here, we discuss the potential functional role of each FVA in voice processing based  
349 on their sulcal locations.

##### 350 4.4.1 aFVA – *Retrieval and integration of semantic and auditory aspects* 351 *of voice information to drive vocal actions*

352 The aFVA is most closely associated with the *half*, which separates the ventral part  
353 of *pars triangularis (area 45)* from *pars orbitalis (area 47/12)* in the anteriormost  
354 part of the inferior frontal gyrus (Sprung-Much and Petrides, 2020). It is also  
355 located near to the *anterior ifs*, which corresponds to the region around the *prts* in  
356 Petrides 2019 (“Atlas of the Morphology of the Human Cerebral Cortex on the  
357 Average MNI Brain - 1st Edition,” book), where area 45 transits anteriorly into area  
358 47/12 (Petrides and Pandya, 2002). Last, it is also related to the *aalf*, which forms  
359 the caudal border of area 45, with area 44 located posteriorly (Sprung-Much and  
360 Petrides, 2020). As such, we propose that aFVA is likely located in the anterior part  
361 of Broca’s speech region (Broca, 1863), and could lie at the transition between  
362 cytoarchitectonic areas 45 and 47/12.

363 This region has access to: 1) higher-order processed semantic and multimodal  
364 inputs from the anterior and middle parts of the temporal lobe via the extreme  
365 capsule frontal-temporal fasciculus (Frey et al., 2008; Petrides and Pandya, 2009,  
366 1988), which constitutes the *ventral speech pathway* (Hickok and Poeppel, 2007) ;

367 2) auditory inputs from the posterior superior temporal cortex via the arcuate  
368 fasciculus (Frey et al., 2014) ; 3) speech motor output areas, such as area 44 and  
369 the ventral premotor areas, which are located immediately posterior to the aFVA.  
370 This connectivity suggests that the aFVA would have a role in retrieving and  
371 integrating both the higher-order semantic and lower-order auditory aspects of  
372 voice information, to drive speech motor actions via the posterior inferior frontal  
373 cortex. Indeed, (Loh et al., 2020) demonstrated activations in this very area as  
374 participants were actively selecting between vocal actions based on vocal/verbal  
375 feedback. This role is likely preserved in non-human primates considering that the  
376 connectivity of area 45 is homologous across humans and monkeys (Loh et al.,  
377 2017).

#### 378 4.4.2 mFVA – High-level control of orofacial-vocal motor actions based on 379 phonological aspects of voice information

380 Our results indicated that the mFVA is most often found close to the *ifs*, at the more  
381 posterior part of the inferior frontal cortex (i.e. close to the *aalf*, *ds*) relative to the  
382 aFVA. The main neighbouring sulci of the mFVA form the boundaries of area 44 of  
383 the *pars opercularis* with *ifs* dorsally, *aalf* anteriorly, and *iprs* posteriorly, while the  
384 *ds* is known to be an axial sulcus within area 44 (Loh et al., 2020; Sprung-Much and  
385 Petrides, 2018). However, notably, in some participants, the mFVA extends into the  
386 area 45 territory (i.e. near to *half* and *ifs- $\partial$* ). We propose that mFVA occupies *pars*  
387 *opercularis*, i.e. area 44.

388 In both humans and monkeys, this region connects to the posterior superior  
389 temporal cortex via the *arcuate fasciculus* (reviewed in (Becker et al., 2021)), and  
390 to the supermarginal gyrus via the *superior longitudinal fasciculus III*. This network  
391 constitutes the dorsal speech pathway (Hickok and Poeppel, 2007) which is  
392 implicated in phonological processing of speech. Apart from having access to  
393 temporal phonological inputs, area 44 (where mFVA is located) is strongly  
394 associated with the speech motor output region in ventral premotor cortex  
395 (Petrides, 2016). As such, functionally, the mFVA would be involved in the  
396 processing of phonological aspects of voice (obtained from the posterior temporal  
397 cortex) to regulate the control over speech/vocal motor production via the ventral

398 premotor area. Congruent with this role, area 44 has been shown to be involved in  
399 both the conditional selection of orofacial and vocal motor acts, as well as the active  
400 processing of vocal and verbal information (Loh et al., 2020). In nonhuman  
401 primates, area 44 has also been demonstrated to be involved in auditory-driven  
402 vocal motor control (*Aboitiz, 2018; Hage and Nieder, 2013*).

#### 403 4.4.3 pFVA – Top-down influence on speech vocal perception

404 The pFVA is consistently located close to the *iprs*, which delimits area 44 anteriorly  
405 and ventral premotor area 6 posteriorly. It is sometimes found close to the *cs*,  
406 where the primary motor area 4 is found, and close to the *ifs*, which separates the  
407 middle frontal gyrus dorsally from the inferior frontal gyrus. Based on these  
408 neighboring sulci, the pFVA is situated in ventral premotor area 6 at the most  
409 caudal part of the inferior frontal cortex. The speech motor representations have  
410 been located in this region (Conant et al., 2014; Penfield and Rasmussen, 1950).  
411 Recent work (Real et al., 2017) reported that the ventral premotor area might  
412 contribute to the top-down perception of speech by generating feedforward  
413 predictive models of speech motor plans which are then compared with perceived  
414 auditory-vocal inputs in the temporal cortex. Ventral premotor cortex is  
415 anatomically connected to the posterior parietal and temporal cortices and is  
416 considered part of the dorsal speech pathway described by Hickok and Poeppel  
417 (Hickok and Poeppel, 2007). As such, the pFVA's role in voice processing would be  
418 in exerting a top-down influence on speech-vocal perception.

419  
420 We can observe that these functional activations found in the human prefrontal  
421 cortex (FVAs) are also found in the frontal lobe of the macaques. To date, no study  
422 has demonstrated functional homology of these activations between the two  
423 species. Only the anterior activation of the temporal lobe (aTVA) has been described  
424 as functionally homologous between the two species (Clémentine Bodin et al.,  
425 2021). Therefore, it would be interesting to investigate whether functional  
426 homology exists in the frontal lobe and to examine whether the activations in  
427 monkeys, like humans, are associated with sulcal anatomy. Furthermore, we can

428 explore to what extent we can hypothesize about the evolution of voice perception  
429 between the two species.

## 430 4.5 Limitations and perspectives

431 Several limitations to our study must be considered. One is that we used an  
432 Euclidean distance in 3D for our comparisons. Given the pronounced folding of the  
433 cortical surface, a geodesic distance on the cortical surface (Le Troter et al., 2012)  
434 might have been more appropriate. Hausdorff (Huttenlocher et al., 1993) or Dice  
435 (Shamir et al., 2018) could be used in our case. However, Dice is a measure of  
436 overlap, which means it relies on delineating both the sulcus and the extent of  
437 activation (which is somewhat arbitrary). On the other hand, Hausdorff distance  
438 would allow us to compute a metric with respect to all parts of the sulcus instead  
439 of the nearest point. Since sulci are complex and variable structures, the  
440 interpretation of the Hausdorff distance would then be difficult, with for instance  
441 normalization issues relative to the variations in the size of the sulcus across  
442 individuals. Computing the Euclidean distance between the peak of activation and  
443 the nearest point from each sulcus has the advantages to avoid the thresholding  
444 effect from the Dice, and the normalization issue from the Hausdorff distance. In  
445 future work, we will consider other metrics and features of the cortical anatomy  
446 such as the sulcal pits (Auzias et al., 2015) and the 'plis de passage' (C. Bodin et al.,  
447 2021). We will also refine and clarify the anatomical characterization of  
448 morphological patterns of the sulci (such as Sprung-Much and Petrides, 2018),  
449 search for relationship with the depth of the sulcus (Bodin et al., 2018), or assess  
450 specifically the morphological variability of prefrontal sulci and a possible match  
451 with function as in (Sun et al., 2012). Another direction for future studies could be  
452 to seek to establish correspondences between the different names of sulci provided  
453 by various atlases.

454

## 455 Conflicts of interest

456 None.

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466

## 467 Credit author statement

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623  
624



625      **A.      Appendices**

626    **A.1 Table: Percentage of simultaneous occurrence of each**  
627    **FVA in the same hemisphere**

628

<b>LEFT</b>	<b>aFVA</b>	<b>mFVA</b>	<b>pFVA</b>
<b>aFVA</b>	-	6,8	6,8
<b>mFVA</b>	-	-	29,7
<b>pFVA</b>	-	-	-
<b>RIGHT</b>	<b>aFVA</b>	<b>mFVA</b>	<b>pFVA</b>
<b>aFVA</b>	-	4,1	4,1
<b>mFVA</b>	-	-	41,9
<b>pFVA</b>	-	-	-

629

630    *For each hemisphere of the 74 participants, we looked at which FVA and in what proportion they were co-*  
631    *activated. For each of these left and right FVA we looked at whether or not they appeared simultaneously.*  
632    *We found that in both hemispheres, mFVA is often activated simultaneously with pFVA (29,7% in the left*  
633    *hemisphere, and 41,9% in the right hemisphere).*

634

635

636

637

## A.2 Table: Number of activations detected in each hemisphere

	LEFT	RIGHT
<b>0 FVA</b>	24,3	27,0
<b>1 FVA</b>	<b>37,8*</b>	28,4
<b>2 FVAs</b>	35,1	<b>41,9*</b>
<b>3 FVAs</b>	2,7	2,7

639 *Percentage of cases for which there are 0, 1, 2 or 3 activations in the left and right hemisphere separately*  
640 *(n=74 participants). We computed inverse binomial tests (2 tests, one for each hemisphere) and a Bonferroni*  
641 *correction ( $\alpha/2$ ) to know if some patterns of activations are significant in the population level. \*: pvalue < 0,05*  
642 *corrected. Beyond the positioning of the functional peaks (a, m, p) we asked ourselves which activation number*  
643 *(0, 1, 2 or 3) is most represented (tab. 3). These were 1 FVA in the left hemisphere (37,8% each), and 2 FVAs*  
644 *in the right hemisphere (41,9%). We made inferential statistics on these data to know if the number of FVAs in*  
645 *each hemisphere is higher than the level of chance: we performed a binomial test on both hemispheres and a*  
646 *Bonferroni correction ( $\alpha/2$ ) to know if these results are significant at the population level and we found that 1*  
647 *FVA in left hemisphere and 2 FVAs in right hemisphere appears more often than the chance level (pvalue <*  
648 *0,05 corr.).*

650 A.3 Table: Different activation patterns observed

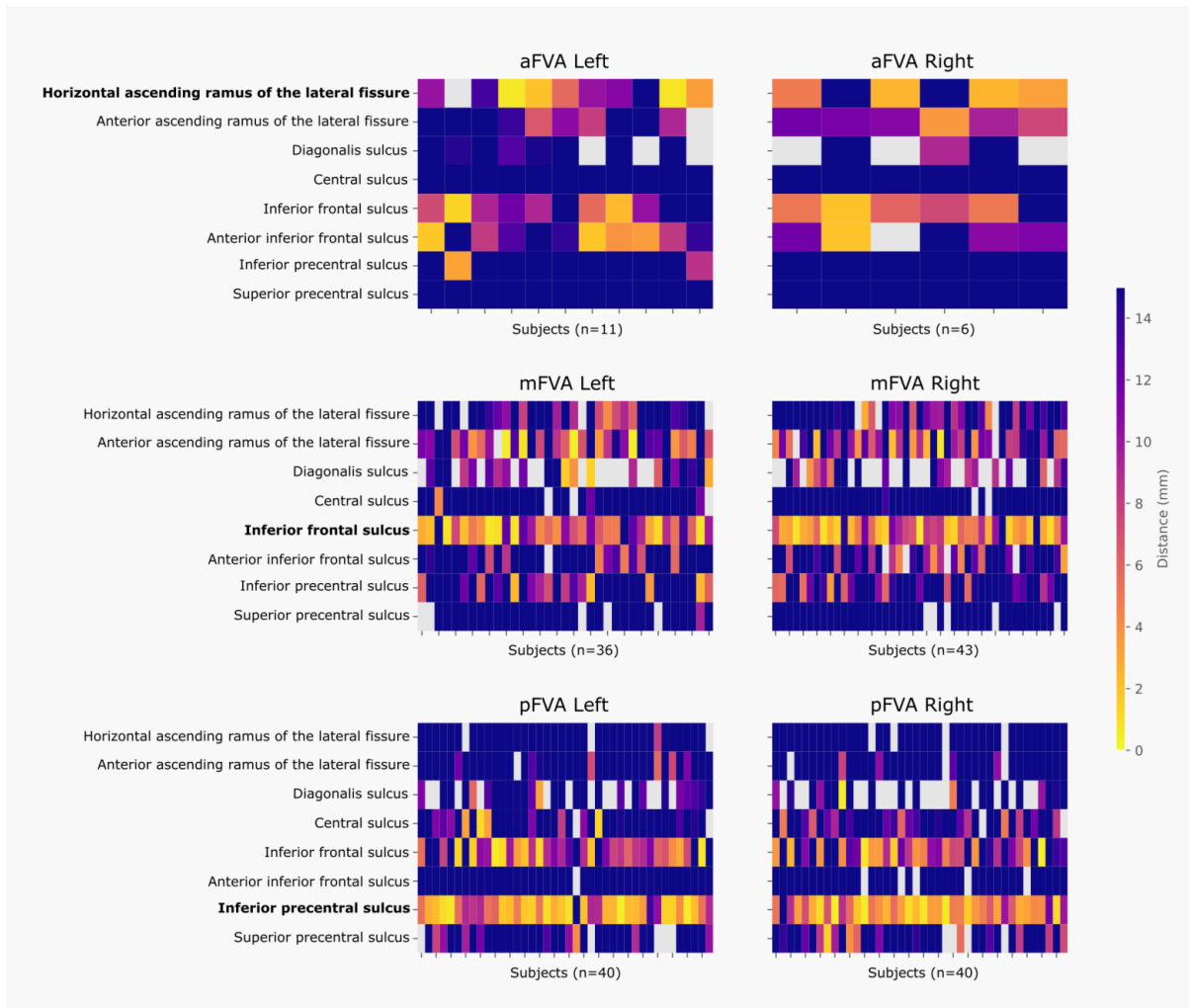
651

		<b>RIGHT</b>			
		<b>0 FVA</b>	<b>1 FVA</b>	<b>2 FVAs</b>	<b>3 FVAs</b>
<b>LEFT</b>	<b>0 FVA</b>	12,2	6,8	5,4	0
	<b>1 FVA</b>	8,1	13,5	14,9	1,4
	<b>2 FVAs</b>	6,8	8,1	<b>20,3***</b>	0
	<b>3 FVAs</b>	0	0	1,4	1,4

652

653 *Percentage of cases for which there are 0, 1, 2 or 3 activations in the left and right hemisphere simultaneously*  
 654 *(n=74 participants). We computed an inverse binomial test and Bonferroni correction ( $\alpha/16$ ) to assess whether*  
 655 *some patterns of activations were significant in the population level. \*\*\*: pvalue < 0,001 corrected*  
 656 *We also confronted each of our patterns (0, 1, 2 or 3 activations) with the same possibilities in the other*  
 657 *hemisphere, to see if we can establish a global pattern of activations (tab. 4). We noticed that the most*  
 658 *represented pattern is 2 activations in the left hemisphere and 2 activations in the right hemisphere (20,3%).*  
 659 *We performed an inverse binomial test and a Bonferroni correction ( $\alpha/16$ ) to know if the results are*  
 660 *significant, and we found that 1 pattern appear significantly: 2 FVAs in both hemispheres is the pattern most*  
 661 *commonly found (20,3%).*

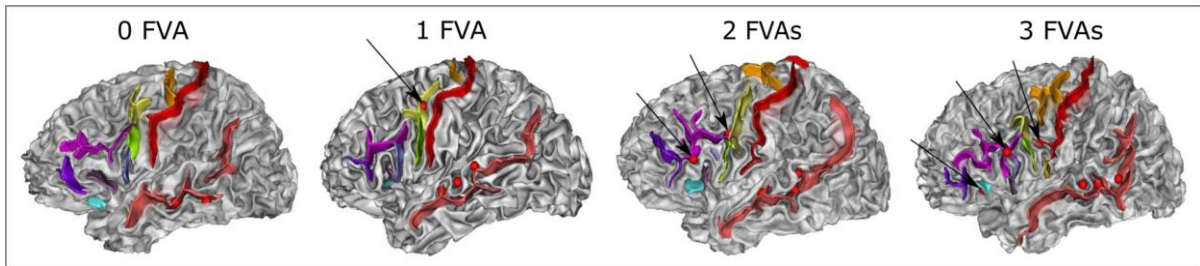
662 A.4 Figure: Distance between sulci of interest and the different  
 663 Frontal Voice Areas



664  
 665 *For each FVA, anterior (aFVA) middle (mFVA) and posterior (pFVA), we measure the distance (mm) to all the 8*  
 666 *sulci of interest, and we plot results on 6 heatmaps. Nearest sulci appear brighter.*  
 667 *Distance measurement between functional activations and the nearest sulcus – In addition to the information*  
 668 *given by the nearest sulcus to the FVAs, we measured the distance between the functional peaks and all sulci*  
 669 *of interest. This study allowed us to assess precisely the organization of the sulci around the functional*  
 670 *activation.*

671

672 A.5 Figure: Examples of individual subjects displaying 0  
673 activation or the 1, 2 or 3 FVAs



674  
675 *For each of the 74 subjects, a significant amount of anatomical and functional variability was observed. Here,*  
676 *we present 4 subjects that represent the 4 different activation patterns: either 0 activation, 1, 2, or 3 FVAs.*  
677