ANATOMO-FUNCTIONAL CORRESPONDENCE IN THE SUPERIOR TEMPORAL SULCUS

C. Bodin [a], S. Takerkart [a], P. Belin [a,c,d], O. Coulon [b,a]

[a] Institut de Neurosciences de la Timone, CNRS UMR7289, Aix-Marseille Université, Marseille, France
[b] Laboratoire des Sciences de l'Information et des Systèmes, CNRS UMR 7296, Aix-Marseille Université, Marseille, France
[c] Centre for Cognitive Neuroimaging, Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK
[d] International Laboratories for Brain, Music and Sound, Department of Psychology, University of Montréal, McGill University, Montreal, QC, Canada

Abstract

The superior temporal sulcus (STS) is an intriguing region both for its complex anatomy and for the multiple functions that it hosts. Unfortunately, most studies explored either the functional organization or the anatomy of the STS only. Here we link these two aspects by investigating anatomo-functional correspondences between the voice-sensitive cortex (Temporal Voice Areas) and the STS depth. To do so, anatomical and functional scans of 116 subjects were processed such as to generate individual surface maps on which both depth and functional voice activity can be analyzed. Individual depth profiles of manually drawn STS and functional profiles from a voice localizer (voice > non voice) maps were extracted and compared in order to assess anatomo-functional correspondences. Three major results were obtained: first, the STS exhibits a highly significant rightward depth asymmetry in its middle part. Second, there is an anatomo-functional correspondence between the location of the voice-sensitive peak and the deepest point inside this asymmetrical region bilaterally. Finally, we showed that this correspondence was independent of the gender and, using a machine learning approach, that it existed at the individual level. These findings offer new perspectives for the understanding of anatomo-functional correspondences in this complex cortical region.

Introduction

Given the key role that voice plays in human communication, it is not surprising to find, in our brain, areas preferentially activated when we perceive voices. These Temporal Voice Areas (TVA) are located along the superior temporal gyrus/sulcus (STG/STS) bilaterally (Belin et al. 2000). They show greater response to vocal sounds, whether they carry speech or not, than to other categories of non-vocal sounds. Despite the great reproducibility of these results using the voice localizer paradigm (Belin, Zatorre, and Ahad 2002; Charest et al. 2013; Ethofer et al. 2012; Kreifelts et al. 2009; Latinus et al. 2013; Pernet et al. 2015), it appears from individual maps that the location of voice-sensitive peaks varies considerably across subjects. However, recent evidence using cluster analysis suggests that individual functional peaks can be organized, almost symmetrically, in three bilateral "voice patches" distributed antero-posteriorly along the STG/STS (Pernet et al. 2015). These patches exhibit distinct levels of activity (Belin et al. 2000; Pernet et al. 2015), and density (Pernet et al. 2015): bilateral middle patches located near the Heschl's gyrus were those having the highest intensity level, which is consistent with initial findings (Belin et al. 2000). In contrast, the right posterior patch showed the highest cluster density, indicating a high concentration of individual peaks in this location that interestingly seems to correspond to the deepest region of the STS (Pernet et al. 2015). However, no study until now has revealed clear anatomical landmarks that could indicate the location of voice-sensitive regions.

At a basic level of description, the STS is described as a long fold divided into an anterior horizontal trunk section (from the temporal pole to the temporo-parietal junction) and posterior ascending branches. This rough subdivision has been found useful by previous authors to investigate anatomo-functional correspondences in the STS. (Kreifelts et al. 2009) observed that the locus of audiovisual integration of emotional stimuli falls at the bifurcation of the posterior branches. In addition to relying on anatomical features, this was the first study

to highlight a functional subdivision of the STS. More recently, Sun et al. (2015) explored the individual variability and found that subjects having a longer STS trunk section also had a more widespread silent-reading activation along the antero-posterior axis of the sulcus. Taken together, these findings suggest that STS anatomy can constitute a good indicator to locate or characterize functional activity. However, given the apparent complexity of the functional anatomy of voice areas (Belin et al. 2000; Belin, Zatorre, and Ahad 2002; Pernet et al. 2015), a finer description of the STS anatomy is required for a better understanding of anatomo-functional correspondences inside these regions.

One potential relevant trait to characterize sulcal anatomy is depth. Indeed, depth fluctuations inside the STS can help to define potential landmarks to segment the sulcus (G. Auzias et al. 2015; Cykowski et al. 2008; Ochiai et al. 2004). Recent evidence shows that the STS, including its trunk section, contains a relatively invariant number of "sulcal pits", which are points of maximum depth within folds being very reproducible across subjects (G. Auzias et al. 2015; Im et al. 2010). Conversely, the STS would also contain an invariant number of "plis de passage" (PP), i.e., annectant gyri buried inside the fold that separate the sulcus into several parts (Ochiai et al. 2004), similar to the "Pli de passage fronto-parietal moyen" within the central sulcus (Boling et al. 1999). Each PP is thought to be more or less superficial across individuals and hemispheres, causing an important source of variability of both depth and visual external aspect of the sulcus. This variability constitutes the second reason why we should investigate STS depth. In addition to giving a fine description (and consequently a segmentation) of the sulcus, the variability of depth landmarks opens the way to the comparison between individuals, genders or hemispheres. A major finding demonstrating this is the STS depth asymmetry. The right STS was found to be deeper than the left STS in a portion ventral to Heschl's gyrus, called the "STAP" (Superior Temporal Asymetrical Pit, (Leroy et al. 2015; Glasel et al. 2011). This asymmetry is highly significant and present

irrespective of age, handedness and language lateralization. However, it is still not known if this anatomical trait is functionally relevant. A correspondence between sulcal depth and a functional area corresponding to the sensory-motor hand representation has been already found in the central sulcus (Boling et al. 1999), and observed qualitatively between voice areas and the STS (Pernet et al. 2015). Thus, and this is the third argument, variability of STS depth could be linked to functional variability in voice areas.

The purpose of the present study is to search for correspondences between functional activity elicited by voice perception and STS depth. To this end, we first constructed STS depth profiles, i.e. the depth fluctuations along the STS antero-posterior axis (Leroy et al. 2015) , of 116 subjects from their cortical surface representation generated by the BrainVisa software (Mangin et al. 2004). Then, we projected individual functional maps from the voice localizer on these same corresponding cortical surface representations (Operto et al. 2008). This allowed us to generate individual functional profiles in the same coordinate space than depth profiles for better comparison. We examined anatomo-functional correspondence first qualitatively at the group level, by comparing functional profiles with depth profiles, then quantitatively at the individual level, by estimating the predictive power of the functional signal to infer the value of anatomical features, using a machine learning approach. We hypothesized that the depth within STS would provide landmarks indicating the location of voice-sensitive activity.

Materials and methods

Subjects

One hundred and sixteen healthy subjects were scanned (n=116; 53 males, 63 females; mean age 23.7 ± 5.8) as part of published and unpublished experiments of the Voice Neurocognition Laboratory (http://vnl.psy.gla.ac.uk/) of the Institute of Neuroscience and

Psychology at University of Glasgow. Participants, drawn mostly from the Glasgow student population, were of various ethnic backgrounds, education and manual lateralization and all provided written informed consent prior to participation. The experiments were approved by the local ethics committee at University of Glasgow. Anatomical analysis was carried out on 95 subjects (51 males, 44 females; mean age 23.9 ± 6.1), whereas functional and anatomo-functional parts were performed on 74 subjects (34 males, 40 females; mean age 23.4 ± 4.9). Exclusion of subjects was due to algorithmic failure for depth or functional profile extraction. All subjects kept for the study had both lower and upper functional profiles in addition to depth profiles.

MRI acquisition

All scans were acquired on a 3T Siemens (Erlangen, Germany) Tim Trio scanner at the Centre for Cognitive Neuroimaging (http://www.ccni.gla.ac.uk/), University of Glasgow.

High resolution 3D T1-weighted sagittal scans were acquired for each subject (voxel size 1 mm3 isotropic; acquisition matrix 256 x 256 x 192).

Functional images were obtained from the voice localizer (Belin et al. 2000; Pernet et al. 2015) constituted of forty 8-sec blocks of either vocal (20 blocks) or non-vocal (20 blocks) sounds. A single-shot gradient-echo echo-planar imaging (EPI) sequence was performed with the following parameters: field of view (FOV) = 210 x 210 mm2, 32 slices per volume, interleaved slices order, voxel size 3 x3x3.3 mm3, acquisition matrix 70x70, flip angle = 77°, echo time (TE) = 30 msec, repetition time (TR)= 2 sec, acquisition time (TA)=2 sec.

Anatomical analysis

Brainvisa pipeline

All anatomical images were post-processed at Neurospin center (Analysis and information processing unit UNATI, NeuroSpin, CEA Saclay, Gif-sur-Yvette) using the *Morphologist* pipeline in the BrainVisa software (Mangin et al. 2004). The pipeline includes the following steps: correction for spatial inhomogeneities in the T1w signal intensity, splitting of the hemispheres, tissue statistics estimation, white-gray matter classification and white matter reconstruction. As a result, an individual triangular mesh representation of the grey/white matter interface was obtained for both hemispheres of all subjects.

STS identification and drawing

The superior temporal sulcus (STS) is a highly distinguishable fold separating the superior from the middle temporal gyrus in the temporal lobe. It consists of extensive – both in width and length- areas of cortex buried in the upper and lower banks of the sulcus. The left and right STS fundi of each subject were drawn semi-automatically on the inner surface of the cortex (grey-white matter interface, *Figure 1.A*) using the SurfPaint module of the Anatomist visualization software (Le Troter, Rivière, and Coulon 2011). We first determined manually the anterior and posterior points of the sulcus based on anatomical landmarks easily identifiable in each subject. The anterior extremity was chosen as the tip of the temporal pole, posterior to polar temporal sulcus. In most cases, this sulcus was perpendicular to the STS and a clearly visible PP separates these two folds (Ochiai et al. 2004). The posterior extremity was chosen as the intersection of the main body of the sulcus with its posterior branches (that were not included).

Finally, the fundus of the STS was drawn automatically between the two extremities, following the deepest path between the two extremities (Le Troter, Rivière, and Coulon 2011). In short, we selected the "stem" of the STS (Bonte et al. 2013; Ochiai et al. 2004) which we call STS thereafter.

Depth profiles

For both hemisphere of each subject, sulcal depth was computed as the geodesic distance from the sulcal fundus to the outer cortex. More precisely, the algorithm selected the shortest path along the cortical surface from the deepest points of the STS to the gyral crowns. (Rettmann et al. 2002). The depth was then sampled at 100 equally spaced locations along the antero-posterior axis of the STS fundus. As a result, two standardized individual depth profiles were extracted (left and right), where 0 represented the anterior extremity and 100 the posterior extremity of the STS fundus for each hemisphere, similar to the standardized depth curves used in Cykowski et al. (2008). An algorithmic failure during this depth profile extraction compelled us to keep only 95 subjects for next anatomical analysis. Once extracted, depth profiles could be easily compared between subjects (*figure 1.A*). An STS depth asymmetry index AI= $2*(R-L)/(R+L)$, where R and L represent right and left depth respectively, was computed for each individual at each STS coordinate. Positive AI values reflected a locally deeper right STS. Significant left-right differences were assessed by using Mann-Whitney non parametric tests across individuals, at each position of the STS axis. The resulting p-values were corrected for multiple comparisons (Bonferroni).

Functional analysis

Voice localizer

Functional images were preprocessed in SPM8 (Wellcome Department of Cognitive Neurology, University College London). It included corrections for head motion, realignment of scans to the first volume, co-registration of the mean EPI image to the corresponding individual anatomical scan and smoothing (Gaussian kernel of 8mm full width at half maximum), as in Pernet et al. (2015).

We then performed first-level (single-subject) analysis using a design matrix that contained separate regressors for vocal and non-vocal sounds (Belin et al. 2000; Pernet et al. 2015), plus realignment parameters to account for residual motion artifacts. Two contrast maps: "Vocal > Non-Vocal" and "All sounds > Silence" were computed per subject.

Surface-based functional maps

Individual 3D functional maps were projected on the corresponding 2D cortical mesh representation (*Figure 1.B*) using the method presented in (Operto et al. 2008), resulting in individual 2D surface-based functional maps.

Inter-subject cortical surface matching was performed using the Hip-Hop method (Auzias et al. 2013) available in the Cortical Surface toolbox in BrainVisa (http://www.meca-brain.org/softwares/). We could then average functional maps across subjects to get a group-level overview of the voice areas localization on the cortex. The average map is represented in *Figure 3*, upper row, on the HipHop138 group template (http://www.meca-brain.org/softwares/hiphop138-cortical-surface-group-template/).

Individual maps were also overlapped with the corresponding STS lines in order to compute functional profiles as described in the next section.

Functional profiles

The surface-based functional map of each individual was used to generate a functional value for each of the 100 sections of the STS line. More precisely, at each coordinate of the STS fundus, functional values were integrated in the direction perpendicular to the STS fundus, across the upper and lower walls, within a distance of 25mm. We showed a posteriori that this distance allowed integrating the highest level of functional activity (*supplementary material figure B*).

This procedure resulted in upper and lower functional values at each STS coordinate and produced, for each hemisphere, an upper and lower functional profile i.e. the functional activity located on the upper and lower walls of the sulcus respectively, as shown in *Figure* 1-B and C. As for depth analysis, an algorithmic failure occurs during functional profile extraction of certain subjects, due to complex triangle configurations on cortical meshes. We finally obtained a set of 74 subjects for which we had both lower and upper functional profiles in addition to depth profiles.

These profiles give information about the functional fluctuations along the STS axis (*Figure 1.C*). In the end, each subject had four functional profiles: right upper (Rup) and lower (Rlow), and left upper (Lup) and lower (Llow). These functional profiles are defined in the same standardized STS axis than depth profiles, thus making them directly comparable.

Mann-Whitney non parametric tests at each [0-100] coordinate were performed to investigate functional asymmetry, between hemispheres or between the two banks of the STS. Resultant p-values were then corrected for multiple comparisons (Bonferroni).

Figure 1 here

Anatomo-functional analysis

The principal question of the present study was: can sulcal depth be a landmark of voice-sensitive functional activity? After characterizing the STS anatomy and functional activity we therefore investigated anatomo-functional relations by comparing depth profiles with functional profiles (*Figure 1.C*). To this aim we first examined if there was an anatomo-functional correspondence at the group level by qualitatively comparing fluctuations of depth and functional average profiles along the STS axis.

We then investigated the links between structure and function at the individual level. To this aim we used a machine learning approach similar to the one used in (Weiner et al. 2014),

based on supervised classification. Here, we asked whether the BOLD signal measured at a given point of the STS could predict whether this point was located 'inside' or 'outside' the STAP, using a simple logistic regression model $f(X)=Y$. The input vector X of our model f was defined as the concatenation of the values of the upper and lower profiles for the « Voice minus Non-voice » contrast. To define the output Y of the model for each subject, we first located the individual deepest point of the STS within the STAP that had been defined at the group level (see Figure 2); then, we defined the region centered on this point with the same width as the group STAP (inside: $y=+1$), and the points outside of this region were labeled with $y=-1$. The generalization performances of the model were assessed by measuring the balanced accuracy (ref) in a 10-fold cross-validation (i.e where we left out one tenth of the subjects for the test set in each fold). Finally, the significance of these results was estimated by repeating this analysis using datasets where the labels y are randomly permuted (N=10000 times), which allowed computing the probability that the null hypothesis of no link between structure and function was valid.

Results

STS depth asymmetry

We found a strong asymmetry of the STS, with a deeper sulcus in the right hemisphere (*Figure 2*). This trend was highly significant (Mann Whitney, $p<0.001$) between coordinates 49 to 93 on the STS axis, and was preserved after Bonferroni correction (Mann Whitney, $p<0.05$). We considered this region of significant asymmetry as the equivalent of the "STAP" (Superior Temporal Asymmetrical Pit) previously described by Leroy et al. (2015). This group-asymmetric segment approximately corresponds to the posterior half of the STS stem. If we consider the whole STS, with its posterior branches, it corresponds to the middle part of the sulcus. In the right hemisphere the STAP corresponds to the deepest region of the sulcus,

whereas in the left hemisphere it corresponds only to a local depth maximum because the deepest region is the intersection of the posterior ascending branches (the posterior extremity in figure 2).

At the individual level, we observed a large variability in depth profiles, due to distinct combinations of "plis de passage" (PP) for each subject. Nevertheless, 82% of our subjects (n=78) showed a global rightward asymmetry, i.e. a positive average index of asymmetry (AI), with a mean AI of +15.4% ± 20. When we computed the mean AI along the STS axis, we found a maximal value at coordinate 68 (*Figure 2*), inside the STAP segment. A second asymmetry peak (AI=12,7 %, coordinate 18) was also revealed in the anterior part of the sulcus, meaning that there is a trend in our population toward a deeper right STS in this region. The presence of a superficial PP was often observed on the left hemisphere in this part of the sulcus and could explain the peak of asymmetry.

Figure 2 here

Temporal voice areas (TVA)

As shown by average functional maps (*Figure 3, top*), the contrast "Voice > Non Voice" showed significant BOLD signal differences on both banks of the STS, as well as within the fold, which is the traditional location of the voice areas (Belin et al. 2000; Pernet et al. 2015). The contrast "All> Silence" (*supplementary material figure A top row*) revealed an activity localized around the upper bank of the STS and the primary auditory cortex.

These observations were found again on averaged functional profiles (*Figure 3, bottom row*). They revealed a higher activity in the upper bank of the posterior STS bilaterally (p<0.05, Bonferroni corrected) for the "Voice>Non Voice contrast". For "All>Silence" contrast,

functional activity is higher on the upper bank than on the lower bank (p<0.05, Bonferroni corrected) and more extended along the STS axis bilaterally.

No significant difference between hemispheres was found at any location along the entire STS axis (p>0.05 Bonferroni corrected). Regarding the peaks of the group-average functional profiles, right voice activity was located at a larger coordinate than on the left side, particularly for the upper bank. Indeed, the functional peaks were respectively located at coordinates: Lup: 58, Llow: 55; Rup: 77, Rlow: 60 on the STS axis (*Figure 3*).

Anatomo-functional correspondence

Our qualitative analysis of average profiles revealed a spatial correspondence between the deepest point of the STS inside the STAP region and the peak of voice activity, for both hemispheres (*Figure 3*). More precisely, for both hemispheres and both upper and lower banks of the STS, the maximum of the average functional profile (Voice>Non Voice) was very close to that of the average depth profile on our STS axis. Knowing that these depth peaks are not identically located in the two hemispheres (Left: 60; Right: 73), the functional peaks are also shifted as previously described (Lup: 58, Llow: 55; Rup: 77, Rlow: 60), suggesting that inter-hemispheric differences are similar for voice-specific functional activity and sulcal depth . To conclude, an anatomo-functional correspondence seems to exist inside the asymmetric region of the STS (STAP), human voice activity being focused into the deepest region of the sulcus. Note that this was not the case for the global auditory activity (All > Silence, *supplementary material Figure A*) where functional peaks are respectively at: Lup: 57, Llow: 44; Rup: 58, Rlow: 52 on the STS axis.

At the individual level, the generalization performance of our machine learning model, i.e. the supervised classification of functional data into 'inside' or 'outside' the individual STAP, was of 61%   and 71%   (average balanced accuracies) respectively in the left and right

hemispheres, which is significantly different from chance level (50%) in both hemispheres (p<0.0001). We can then examine the behavior of the model at the points of maximal activity, specifically by testing whether it predicts whether these points are located inside the STAP individually: the maximum of left (Linf) and right (Rinf) inferior profiles were located in the individual STAP in 56.8% and 73% of the subjects respectively, whereas the maximum of left (Lsup) and right (Rsup) superior profiles were both located in the STAP in 100% of the subjects. These results therefore quantitatively demonstrate the anatomo-functional correspondence at the individual level.

Figure 3 here

Gender comparison

We performed additional analysis to examine whether previous findings were modulated by subject gender. There were no significant differences between respective left and right STS depth profiles of males and females (*Figure 4*). Both groups had a significant (p<0.05, Bonferroni corrected) asymmetrical STAP region (between 51 and 90 for males, 55 to 90 for females).

Contrary to depth, functional profiles showed a trend towards an influence of gender. Indeed, *Figure 4* shows several portions of the STS where the functional profile of females differs from that of males (p<0.05 uncorrected, plotted in blue for upper profiles, green for lower ones). These portions are more extended for upper profiles, and the differences always reflect higher activity in females than in males. These trends did not survive Bonferroni correction, however.

Noteworthy, the anatomo-functional correspondence between the deepest points of the STS and the peaks of voice activity found in the entire sample is clearly visible in each gender

group. The average depth peaks inside respective STAP regions were located at Left: 61; Right: 73 for females and Left: 55; Right: 76 for males. The average functional peaks were located at : Lup: 72, Llow: 54; Rup: 77, Rlow: 59 for females and Lup: 63, Llow: 57; Rup: 74, Rlow: 53 for males on the STS axis.

Figure 4 here

Discussion

The present study is the first to demonstrate a link between STS depth and functional activity in the temporal voice areas. We used an innovative method that first allowed us to finely characterize depth anatomy of the STS and to replicate the finding by Leroy et al (2015) of a strong asymmetry in its middle part (the STAP, *Figure 2*). Then, to compare depth and functional profiles in a common referential and to highlight an anatomo-functional correspondence between the voice-sensitivity maxima and depth maxima inside the STAP region of the STS (*Figure 3*). Finally, we demonstrated that this correspondence was present irrespective of hemisphere side and subject gender (*Figure 4*) and could be found at the individual level too.

STS depth characterization

We found that the STS is highly asymmetric ($p<0.001$) in most of our subjects (82%) with a deeper right STS in a middle portion of the sulcus (*Figure 2*). This landmark seems to correspond to the STAP initially described in Leroy et al. (2015) and fits with previous reports of a rightward STS asymmetry (Bonte et al. 2013; Leroy et al. 2015; Li et al. 2014; Van Essen 2005; Im et al. 2010; Ochiai et al. 2004). As in previous investigations (Leroy et

al. 2015; Bonte et al. 2013), the STAP found here represented a large part of the STS trunk section, with a right peak deeper than 20 mm, and was present irrespective of the gender.

The method used here for the STS exploits the 'depth profiles' representation previously validated on the central sulcus (CS) (Cykowski et al. 2008; Hopkins et al. 2014). However, instead of extracting automatically the sulcus as 3D object, as done in anatomical studies of the CS (Cykowski et al. 2008; Hopkins et al. 2014; Sastre-Janer et al. 1998) and the STS (Glasel et al. 2011; Leroy et al. 2015; Ochiai et al. 2004), we performed a semi-automatic drawing of each individual sulcus. This approach presents several advantages: first, the semi-automatic drawing avoids possible misidentification of sulci: merging can occur between the STS and adjacent sulci, disrupting automatic sulcal identification. Second, defining the anterior and posterior extremities of the STS trunk in a consistent manner is extremely difficult automatically, which is why we favored a manual selection. Third, the 2-dimensional sulcal line constructed by our method can go through sulcal interruptions over the PPs, resulting in a single connected line, while automatic representations are segmented in several pieces (Ochiai et al. 2004). Finally and crucially, functional activity can be more easily projected on this 2D sulcal line and analyzed in the same referential.

Because of these advantages and given the fact that our results are in line with those of previous studies, we argue that the semi-automatic method is well adapted to study anatomo-functional correspondence.

Anatomo-functional correspondence between STS pit and voice-sensitivity maxima

The first question in this study sought to determine if STS depth could be related to voice-sensitive functional activity, and potentially provide landmarks of this activity. Several reports have shown that the functional activity elicited by human voice perception peaks in the middle region of the STS (Belin et al. 2000; Deen et al. 2015; Kreifelts et al. 2009) or,

similarly, at the level of the middle cluster of TVAs (Pernet et al. 2015). However, for the first time, we highlighted a more accurate localization of this functional peak based on anatomical landmarks. We found a bilateral spatial correspondence between the STS depth peak inside the STAP region and the functional peak of voice-sensitive activity (*Figure 3*). By looking at surface-based functional maps and considering the location of the STAP (Leroy et al. 2015), we can see that this spatial correspondence occurs, on the length axis, at a middle section of the entire sulcus corresponding to the 'posterior sulcal root' (Ochiai et al. 2004) ventral to the planum temporale. In order to localize this correspondence on the depth axis, we integrated repeatedly the voice-related activity within an increasingly large distance from the STS fundus. Results showed that the peaks were located on the top of right STS banks, around 20 mm from the sulcal fundus. However, on the left hemisphere, the peaks were located beyond the upper bank but also in the fundus of the STS (*supplementary material figure B, maps figure 3*). Hence, the depth peaks of the STS within the STAP constitute landmarks that indicate the position of voice functional peaks along the STS length axis. This landmark has the same localization value than the 'hand-knob' or the 'Pli-de-passage fronto-parietal moyen' used to localize the primary hand motor area along the length of the central sulcus (Yousry et al. 1997; Boling et al., 1999).

The anatomo-functional correspondence was found in both hemispheres and both sulcal banks, but functional differences could be noticed between these cortical regions. On one hand, we did not find significant differences in functional activity between the two hemispheres ($p > 0.05$ Bonferroni corrected), but found a trend towards a higher activity on the right side, confirming previous results (Belin et al. 2000; Pernet et al. 2015). On the other hand, we found that activity was higher in the upper bank of the STS (*Figure 3*) compared to the lower bank. This could be explained by a greater recruitment of the STG rather than MTG during voice perception (Belin et al. 2000; Deen et al. 2015; Pernet et al. 2015). Only

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differences in the posterior part of the STS survived statistical corrections, meaning that in this region the upper bank of the STS (STG) is much more recruited than the lower bank (MTG). This trend could be driven by the vertical orientation of the posterior sylvian fissure: the activity would follow the STG rather than ventral regions, which seem more implicated in face perception (Deen et al. 2015; Pelphrey et al. 2005).

Another important finding was that the anatomo-functional correspondence was found in both genders (*Figure 4*). However, one unanticipated result was that females exhibited higher voice activity than males in several portions of the STS (p>0.05 uncorrected). Only one study (Arhens et al. 2014) describes a gender effect in temporal voice areas by using multivariate pattern analysis. They showed a better vocal/non vocal classification in females than in males in the middle parts of bilateral MTG and the right STG. Here, this trend could be related to the fact that we found gender differences between both lower profiles and upper profiles along the STS axis. This raises interesting questions regarding the possible influence of anatomy on this different functional sensitivity to voice between genders. []

Finally, we demonstrated that the anatomo-functional correspondence exists at the individual level. Although simple correlation methods did not highlight significant results, machine learning techniques were able to individually predict the depth-relative position of an STS point based on functional information. Indeed we demonstrated that, for the majority of subjects, the maximal functional peak was located inside their individual STAP. Crucially, this correspondence was found in all subjects if we take into account the upper bank of the STS. This finding, while preliminary, supports the idea of an STS depth landmark for voice-sensitive activity previously suggested by the qualitative results (*Figure 3*). Nonetheless there are still many unanswered questions about the link between depth and function.

What link between STS depth and voice-related activity?

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The anatomo-functional correspondence found here does not allow us to infer if depth and voice sensitive activity are causally linked. However, several points can be addressed because they could directly or indirectly link these two features, for example during development.

On one hand, we know from previous studies that voice perception is already functional in infants and even in neonates (Kisilevsky et al. 2003; Ockleford et al. 1988) and that a voice-sensitive cortex is already present in 3-month-old infants (Blasi et al. 2011; Grossmann et al. 2010). On the other hand, anatomical studies showed that a deeper right STS is already observable in fetuses (Kasprian et al. 2011) and persists throughout the human lifespan (Bonte et al. 2013; Glasel et al. 2011; Leroy et al. 2015). Taken together, these reports suggest that the establishment of the depth asymmetry of the STS and its sensitization to human voice occur very early during the prenatal life, and that the cortex in this region becomes really selective to voice perception during infancy.

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A key region in a deep sulcus

The fact that the most voice-sensitive region is located at the level of an asymmetrical and deep part of the sulcus might be more than mere coincidence. Indeed this STS region, as a sulcal pit, is supposed to gather several key features that would make it particularly interesting.

First of all, sulcal pits have been shown to be highly heritable and reproducible across subjects, with a more pronounced effect in deeper sulci (G. Auzias et al. 2015; Im et al. 2010; Lohmann et al. 1999). Obviously, this cannot be segregated from the hierarchical emergence of folds during development (Chi, Dooling, and Gilles 1977; Lohmann et al. 1999).The STS

has been shown to be a primary fold appearing early in the development (Chi, Dooling, and Gilles 1977; Dubois et al. 2008) with a rapid growth of depth during the first years of life (Meng et al. 2014). Crucially, its asymmetry is already present in utero and persist until adulthood (Glasel et al. 2011; Kasprian et al. 2011; Leroy et al. 2015). The importance of these results is twofold: first, the most voice-sensitive cortex is located in a region that is stable both inter- and intra-individually. Second, the depth of this region is still evolving during the first years of life, a period which is crucial for vocal social interactions. Conversely, voice perception is early developed in humans (Kisilevsky et al. 2003; Ockleford et al. 1988), and is a primitive ability shared with others species including its cerebral substrate (Andics et al. 2014; Petkov et al. 2008; Sadagopan, Temiz-Karayol, and Voss 2015). Thus, it can be proposed that the location of the voice activity is in good agreement by the stable and primitive nature of the depth pit.

Another feature that can play a role in the anatomo-functional correspondence observed in this paper is the structural connectivity. In the key study of Leroy et al. (2015), the authors revealed an effect of callosal connectivity on the STS asymmetry, and suggested that the white matter fibers may constrain the folding anatomy. However, given that the asymmetry was reduced but not absent in corpus callosum agenesis and according to new hypothesis on gyrification (Ronan and Fletcher 2015; Xu et al. 2010), we cannot assert that the sulcal pit within the STAP region is only impacted by structural connectivity. Rather, we can hypothesize that white fibers may be a factor among others that influence the depth of the STS during first years of life (Meng et al. 2014), and that this influence would be heterogeneous along the STS like sensitivity for voice is heterogeneous.

Finally, the voice-sensitive region described in this study could be located in a functional strategic place. At the whole brain scale, STS appears as a hub region for both social perception (Allison, Puce, and McCarthy 2000; Lahnkoski et al. 2012) and language, between

the ventral and the dorsal streams (Hickok and Poeppel 2007). At a smaller scale, the sulcal pit of interest here is located functionally near the primary auditory cortex on Heschl's gyrus, and anatomically close to the intermediate PP (Ochiai et al. 2004). This sulcal interruption was previously described as asymmetric, with a PP much more superficial in the left STS compared to the right (Ochiai et al. 2004). Nevertheless, the functional significance of these sulcal bridges is interesting and need to be further explored, in line with the observation that three main PP are crossing the STS similar to the three voice patches described along this sulcus (Pernet et al. 2015).

Individual variability and future work

Finding anatomo-functional correspondences is a very difficult task considering the large individual variability. We encountered two sources of variability in this study: the first one was anatomical and concerns essentially the presence of PP inside the sulcus that exhibit variable levels of depth (Ochiai et al. 2004; Leroy et al. 2015) depending on the subject and the hemisphere. These PP can strongly modify the aspect of two individual depth profiles and make the detection of the depth pit harder. [] The second source of individual variability was functional and derives from the considerable spatial variability of voice-sensitive peaks (Pernet et al. 2015). Individual functional profiles revealed several voice peaks along the STS and the highest one was not necessarily the one observed at the group level (*Figure 3*).

Several improvements could be made for future investigations. First, it might be possible to use other landmarks on the STS in addition to the extremities (see *Figure 2*). This could improve the alignment of both depth and functional profiles between subjects. For example, a strategy would be to label stable gyri around the STS (as in Glasel et al. 2011; Leroy et al. 2015), or the PP, whose number has been shown to be constant across individuals despite variable depth levels (Ochiai et al. 2004). Along the same line, other sulcal features than

depth could be studied, such as variable morphological traits that could be linked to functional variability, as done by Sun et al. (2015). In this work, the authors characterized both anatomical and functional individual variability and found correspondences based on correlation analysis.

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Figures captions

Figure 1: Schematic description of the methods that were used in the paper. (A) The superior temporal sulcus (STS) was manually drawn on the cortical mesh of each subject. Depth values were computed and standardized on a common coordinate axis to build the depth profiles. (B) Functional voice > non voice maps were individually projected on the cortical surface. Functional profiles were built by integrating functional activity from the upper and the lower bank of the STS at each coordinates of the STS previously drawn. (C) Anatomo-functional correspondence was investigated by comparing the two types of profiles.

Figure 2: STS depth asymmetry. Group-average (± SEM) depth profiles of the right (in red) and left (in blue) STS, with depth values (mm) on the left vertical axis. The group-average index of asymmetry (AI %) is shown in black dotted line with values on the right vertical axis. Horizontal dotted line indicates null AI value. The most significant portion of right-left asymmetry (Mann-Whitney, p<0.001) is represented by the orange overlay and illustrates the STAP (superior temporal asymmetrical pit, Leroy et al. 2015).

Figure 3: Anatomo-functional correspondence in the STS. *Top panel:* Averaged surface-based functional maps of the voice areas projected on the HipHop138 template for the left (L) and right (R) hemisphere. The color bar indicates the mean t value of the functional activity. *Lower panel:* Anatomical (black dotted line) and functional (blue line for upper profile and green line for lower profile (± SEM) averaged profiles were represented together with the STAP region (orange overlay). The stars line indicates the significant upper-lower differences along the STS (Mann-Whitney, p<0.05 Bonferroni corrected).

Figure 4: Effect of gender on STS asymmetry and function. Anatomical (black dotted line) and functional averaged profiles (blue line for upper profile and green line for lower profile (± SEM) were represented together with the STAP region (orange overlay) for females (*top panel*) and males (*lower panel*). The blue stars line indicates the significant gender differences along the STS for upper profiles whereas the green stars line indicates the significant gender differences along the STS for lower profiles (Mann-Whitney, p<0.05 uncorrected).