

1 Improving a probabilistic 2 cytoarchitectonic atlas of auditory 3 cortex using a novel method for 4 inter-individual alignment

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14
15 **Abstract** The human superior temporal plane, the site of the auditory cortex, displays a high
16 inter-individual macro-anatomical variation. This questions the validity of curvature based
17 alignment (CBA) methods for in vivo imaging data. Here, we have addressed this issue by
18 developing CBA+, which is a cortical surface registration method that uses prior macro-anatomical
19 knowledge. We validate this method by using cyto-architectonic areas on ten individual brains
20 (which we make publicly available). Compared to volumetric and standard surface registration,
21 CBA+ results in a more accurate cyto-architectonic auditory atlas. The improved correspondence of
22 micro-anatomy following the improved alignment of macro-anatomy validates the superiority of
23 CBA+ compared to CBA. In addition, we use CBA+ to align in vivo and post mortem data. This allows
24 projection of functional and anatomical information collected in vivo onto the cyto-architectonic
25 areas, which has potential to contribute to ongoing debate on the parcellation of the human
26 auditory cortex.

27 **Introduction**

28 Historically, there has been a substantial effort to describe the micro-anatomy of the human
29 auditory cortex (*Von Economo and Horn, 1930; Galaburda and Sanides, 1980; Rivier and Clarke,*
30 *1997; Morosan et al., 2001; Wallace et al., 2002; Morosan et al., 2005; Clarke and Morosan, 2012;*
31 *Nieuwenhuys, 2013*). Various parcellation schemes have been proposed, which identify a primary
32 area (core; primary auditory cortex) as well as secondary belt and tertiary parabelt auditory areas
33 (*Rivier and Clarke, 1997; Moerel et al., 2014*). The primary auditory cortex (PAC) is generally located
34 on the medial two-thirds of Heschl's Gyrus.

35
36 It has proven challenging to use these results to identify auditory areas in individuals in vivo,
37 as classical cyto- (and myelo-) architectural approaches are limited by the absence of an objective
38 metric defining cyto-architectonic areas. In addition, relating micro-anatomical characteristics to

39 macro-anatomy is hampered by the inherent two-dimensional representation of the results (i.e.
40 by means of drawings or labelled slices) and scarce information regarding inter-subject variability.
41 Instead, observer independent methods for the analysis of serial cyto-architecturally stained
42 sections, that additionally correct for shrinkage artifacts typical of histological processing (**Amunts**
43 **et al., 2000**), have been developed in the last 20 years (**Schleicher et al., 1999**). Using this method,
44 **Morosan et al. (2001)** identified various auditory areas in the superior temporal cortex and gen-
45 erated a probabilistic atlas based on ten individual brains. This atlas (**Eickhoff et al., 2005**) allows
46 assigning probabilistic values to in vivo brain images and has been used to, for example, validate
47 the delineation of PAC on the basis of in vivo MRI images whose contrast is related to myelin (**Dick**
48 **et al., 2012**).

49 The probabilistic atlas is generated using a volume registration method. Instead, the exception-
50 ally reliable correspondence between micro- and macro-anatomy known to be present in many
51 cortical areas (**Turner, 2013**) has inspired the use of registration methods that rely on cortical
52 surfaces and macro-anatomical landmarks such as the major gyri and sulci (i.e. curvature based
53 alignment rather than the whole volumetric data (**Fischl et al., 1999, 2008; Frost and Goebel, 2012;**
54 **Goebel et al., 2006**)). Surface based alignment methods have been shown to improve the accuracy
55 of inter-individual registration in micro-anatomically defined primary motor cortex (**Fischl, 2013**),
56 the human middle temporal area (hMT) (**Frost and Goebel, 2013**), and to improve the registration
57 of a cyto-architectonic atlas of the ventral visual system (**Rosenke et al., 2018; Fischl et al., 2008**).

58 Curvature based alignment is also routinely used in studies investigating the functional and
59 anatomical properties of auditory cortical areas. However, Heschl's Gyrus substantially varies in
60 shape across individuals and across hemispheres, and slight changes in the primary auditory cortex
61 location have been reported in subjects with a typical morphological variation of the Heschl's Gyrus
62 (**Heschl, 1878; Rademacher et al., 1993; Hackett et al., 2001; Marie et al., 2015**).

63 Given this variation in superior temporal plane macro-anatomy across individuals and shift of
64 micro-anatomical areas with macro-anatomy, it is debatable if curvature based alignment improves
65 the correspondence of micro-anatomically defined auditory areas. Accordingly, here we applied
66 curvature based alignment (abbreviated as CBA), as well as a procedure tailored to the temporal
67 lobe by incorporating anatomical priors (abbreviated as CBA+), and reconstructed cortical surfaces
68 from the data of **Morosan et al. (2001)** in order to investigate to what extent maximizing macro-
69 anatomical inter-individual alignment improves the overlap of micro-anatomically defined auditory
70 cortical areas. Our results address if the use of CBA or CBA+ is justified when considering the
71 functional properties of auditory cortical areas. Thereby, our results not only test the validity of
72 the use of CBA in previous studies, but also offer CBA+ to improve across participant alignment
73 of the superior temporal plane as a tool to the auditory community. We showcase this approach
74 by applying CBA+ to an in vivo dataset collected at 7 Tesla and projecting the improved cyto-
75 architectonic atlas onto functional and anatomical group maps. In addition, in order to contribute
76 to the ongoing debate on the in vivo localization of auditory cortical areas (**Moerel et al., 2014;**
77 **Besle et al., 2018**), we align the cyto-architectonic atlas (and in vivo data) to a recent temporal lobe
78 parcellation based on in vivo measurements (**Glasser et al., 2016**).

79 Results

80 We obtained cyto-architecturally labeled temporal cortical areas and post mortem MR images
81 of ten brains (volumetrically aligned (rigid body) to the Colin27 space) used in the JuBrain cyto-
82 architectonic Atlas (**Amunts and Zilles, 2015**). The cyto-architecturally labeled areas were TE
83 1.0, TE 1.1, and TE 1.2 from **Morosan et al. (2001)**, TE 2.1 and TE 2.2 from **Clarke and Morosan**
84 **(2012)**, TE 3 from **Morosan et al. (2005)**, and STS 1 and STS 2 from **Zachlod et al. (2020)**. In order
85 to perform cortex based alignment, the white matter - gray matter boundary was segmented in
86 all ten post mortem brains. To obtain such segmentation, we have used a combination of image
87 filtering techniques and a histogram based segmentation approach (**Gulban et al., 2018b**), which
88 reduced the amount of required manual corrections (see Methods section). Cortical surfaces were

89 reconstructed to perform three different types of group alignment methods. These methods were
90 rigid body (i.e. considering surface sampling [compared to volumetric alignment] and rigid body
91 registration), curvature based alignment (CBA) and curvature based alignment with anatomical
92 priors (CBA+; including the anterior Heschl's Gyrus, the superior temporal gyrus, the superior
93 temporal sulcus, and the middle temporal gyrus as anatomical priors). We additionally compared
94 these surface approaches to the original volumetric alignment in the Colin27 space. We have
95 validated the performance of these methods by comparing the overlap between cyto-architectonic
96 areas across individuals. We subsequently used CBA+ to create superior temporal cortical group
97 maps of in vivo MRI (at 7T) measurements and to align them to the probabilistic cyto-architectonic
98 atlas.

99 **Comparison between alignment methods**

100 **Figure 1** rows 1 and 3 show the averaged curvature maps after alignment with each of the surface
101 approaches we used (i.e., rigid only that linearly coregisters the surfaces, standard CBA, and CBA
102 tailored to the temporal lobe [CBA+]). In the temporal lobe, the increased sharpness of the average
103 curvature maps indicates the improved correspondence of the macro-anatomical features in CBA
104 and CBA+ compared to the rigid only alignment. Especially in the right hemisphere (third row in
105 **Figure 1**), an improvement of CBA+ over standard CBA is noticeable at the level of the Heschl's
106 Gyrus (indicated by a red circle). The improvement in alignment of the macro-anatomical features
107 in the temporal lobes (left and right) is also visible when considering the folded average meshes
108 of the ten brains in the post mortem dataset (i.e. average folded meshes, **Figure 1** rows 2 and
109 4). In absence of large macro-anatomical differences across the individuals, improved alignment
110 should increase the 3D complexity (e.g. gyri and sulci appearing very clearly distinguishable) of the
111 average folded mesh. Cortical curvature-based alignment procedures, however, may be affected
112 when individual cortical macro-anatomy strongly deviates from the average morphology. In the
113 post mortem sample we analyzed, we observed macro-anatomical variations across hemispheres
114 of two types. First, following the characterization described in *Kim et al. (2000)*; *Da Costa et al.*
115 *(2011)*, the number of Heschl's Gyri varied. In particular, we observed 1, 1.5 and 2 Heschl's Gyri
116 in [5, 4, and 1, respectively] right hemispheres and [6, 2, and 2, respectively] left hemispheres.
117 Second, we observed the presence of three hemispheres (one right and two left ones) whose
118 single Heschl's Gyrus was continuous at the anterior part of the anterior temporal convolution,
119 resulting in a split superior temporal gyrus (i.e. interrupted by an intermediate sulcus between the
120 anterior and posterior part with respect to the location of the Heschl's Gyrus - **Figure 13** lower right
121 panel). This rare morphological pattern was first described in *Heschl (1878)* and was reported to
122 occur % 10 of all brains inspected by Richard L. Heschl (110 of 1087 brains). It was 18 times more
123 likely to occur on the left hemisphere in comparison to right (also see *Rademacher et al., 1993*, for
124 another reference to Heschl's work in English). As expected, the tailored alignment we developed
125 here results in a more prominently defined Heschl's Gyrus in the average mesh, resulting from
126 the correct alignment of the anterior Heschl's Gyrus across individual hemispheres. In the split
127 superior temporal gyrus cases, we defined the gyrus as continuous (i.e. bridging the intermediate
128 sulcus). While this definition did not compromise the alignment of the anterior Heschl's Gyrus, the
129 impact of the approach we followed in the alignment of regions in proximity to the intermediate
130 sulcus would require a larger sample on which to evaluate alignment separately according to this
131 macro-anatomical variation (i.e. aligning separately individuals with a split/continuous superior
132 temporal gyrus).

133 To evaluate the effect that minimizing macro-anatomical differences (as evidenced by the
134 improved average curvature maps and folded meshes) has on micro-anatomy, we considered the
135 inter-individual overlap of the cyto-architectonically-defined areas. In **Figures 2-7** we present (for
136 each labelled area) probabilistic maps (after alignment) indicating the number of subjects for which
137 a given vertex is labelled as belonging to the same cyto-architectonic area. For all cyto-architectonic
138 areas, CBA+ improves the overlap (as indicated by the increased probability of a vertex to be labelled

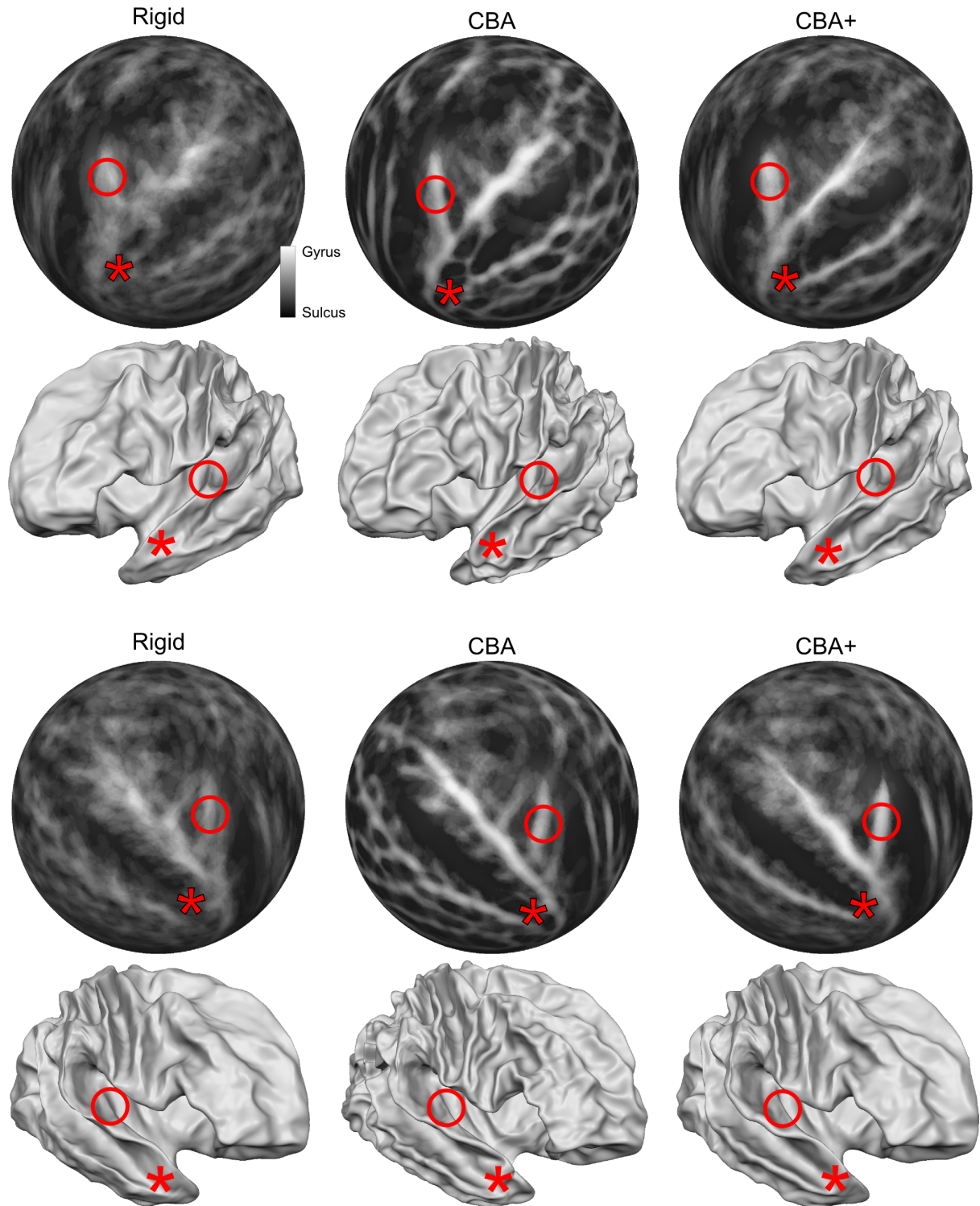


Figure 1. Differences between spherical rigid body alignment, curvature based alignment (CBA) and curvature based alignment with an anatomical prior (CBA+) on group average binarized curvature maps visualized as half-sphere projections (rows 1 and 3) and group average vertex coordinates visualized as folded surfaces (rows 2 and 4). In rows 1 and 3, higher contrast between sulci (dark gray) and gyri (light gray) shows more overlap around Heschl's Gyrus which indicates that a method better accounts for inter-subject morphological variation. In rows 2 and 4, the average vertex coordinates show a more pronounced Heschl's Gyrus in 3D as the alignment methods improves the anterior Heschl's Gyrus overlap.

139 as belonging to same area across the ten brains).

140 To better understand the differences between methods and quantitatively compare the rigid
141 alignment, CBA, and CBA+ surface approaches to the initial volumetric alignment (in Colin27 space),
142 **Figure 8** and **Figure 9** present the histograms of the probabilistic maps of each area (left and right
143 hemisphere, respectively). For the cyto-architectonic areas along Heschl's Gyrus (Te1.0, Te1.1 and
144 Te1.2) the largest overlap is provided by CBA+, which improves micro-anatomical correspondence
145 compared to the volume based alignment and the two other surface approaches we evaluated.
146 For the areas in the planum temporale (Te2.1 and Te2.2), all surface approaches improve micro-
147 anatomical correspondence compared to the volume alignment, and CBA+ provides an additional
148 benefit especially for the area Te2.1. Similarly, for the areas in the superior temporal gyrus and
149 sulcus and middle temporal gyrus (Te3, STS1 and STS2), all surface approaches improve micro-
150 anatomical correspondence compared to the volume alignment while differences between standard
151 CBA and CBA+ are modest.

152 **Aligning in vivo group measures to the probabilistic post mortem areas**

153 The definition of probabilistic cyto-architectonically defined areas has been previously used to
154 analyze in vivo functional and anatomical data (see e.g. (*Dick et al., 2012*)). Here we demonstrate
155 the use of CBA+ and the improved version of the cyto-architectonic atlas to this end. In particular,
156 we aligned in vivo data collected at 7 Tesla to the CBA+ aligned post mortem cyto-architectonic
157 atlas. We considered only the areas in the superior temporal cortex (Te1.0, Te1.1, Te1.2, Te2.1, Te2.2
158 and Te3) as they were consistently included in the imaged field of view in the in vivo dataset. First,
159 we used CBA+ to produce an average morphology for the in vivo data. This alignment allowed us
160 to derive group level maps based on the available anatomical and functional data. In particular,
161 anatomical MRI data (0.7 mm isotropic) were used to derive intra cortical contrast related to
162 myelin from the division of T_1w and T_2^*w data. In addition, functional MRI data (1.1 mm isotropic)
163 collected by presenting natural sounds and analyzed with an fMRI encoding approach (*Moerel*
164 *et al., 2012*), were used to derive tonotopic maps (see **Figure 10**). Second, using CBA+, we aligned
165 the average morphology of the in vivo data to the cyto-architectonic atlas. This allowed us to project
166 cyto-architectonic parcels on the in vivo maps and evaluate their relationship.

167 Intra-cortical contrast related to myelin highlights the (medial) Heschl's Gyrus as the most
168 myelinated region in the temporal cortex (see **Figure 10**). Across cyto-architectonic areas, Te1.0
169 shows the highest myelination contrast. Myelin related contrast is also high in the most medial
170 portion of Heschl's Gyrus (Te1.1) and gradually decreases when moving away from Heschl's Gyrus.

171 The average tonotopic pattern highlights the Heschl's Gyrus as, for the most part, preferring
172 low frequencies, while surrounding areas (in posterior antero-medial and antero-lateral directions)
173 prefer high frequencies (see **Figure 10**). The high frequency areas form an inverted "V" pattern
174 surrounding the Heschl's Gyrus (*Da Costa et al., 2011*; *Moerel et al., 2014*). Cyto-architectonic
175 primary cortical areas (Te1) cover the Heschl' gyrus, with the core (Te1.0) in its middle section
176 which (at the group level) appears characterized by mainly low frequency preference (see **Figure 10**).
177 Located medial to Te1.0, area Te1.1 may reflect an intermediate processing stage between primary
178 and belt areas (*Moerel et al., 2014*) and covers one tonotopic gradient going from high to low on an
179 antero-medial to postero-lateral direction. Te2.2 covers a posterior portion of the tonotopic gradient
180 running in the posterior to anterior direction. Te2.1, covering an intermediate location between
181 Te2.2 and Te1.0/Te1.2, overlaps with a low frequency preferring region in the lateral portion of the
182 Heschl's sulcus. Finally, Te3 covers a low frequency portion of the tonotopic maps along the superior
183 temporal gyrus (*Moerel et al., 2014*). For comparison, in a supplement to **Figure 10** we report the
184 same maps aligned with an atlas obtained from in vivo MRI data (using both anatomical and
185 functional information) in a large cohort (*Glasser et al., 2016*). A direct comparison between the
186 post mortem and in vivo atlases projected on the average anatomical curvature of our in vivo data
187 is reported in **Figure 11**.

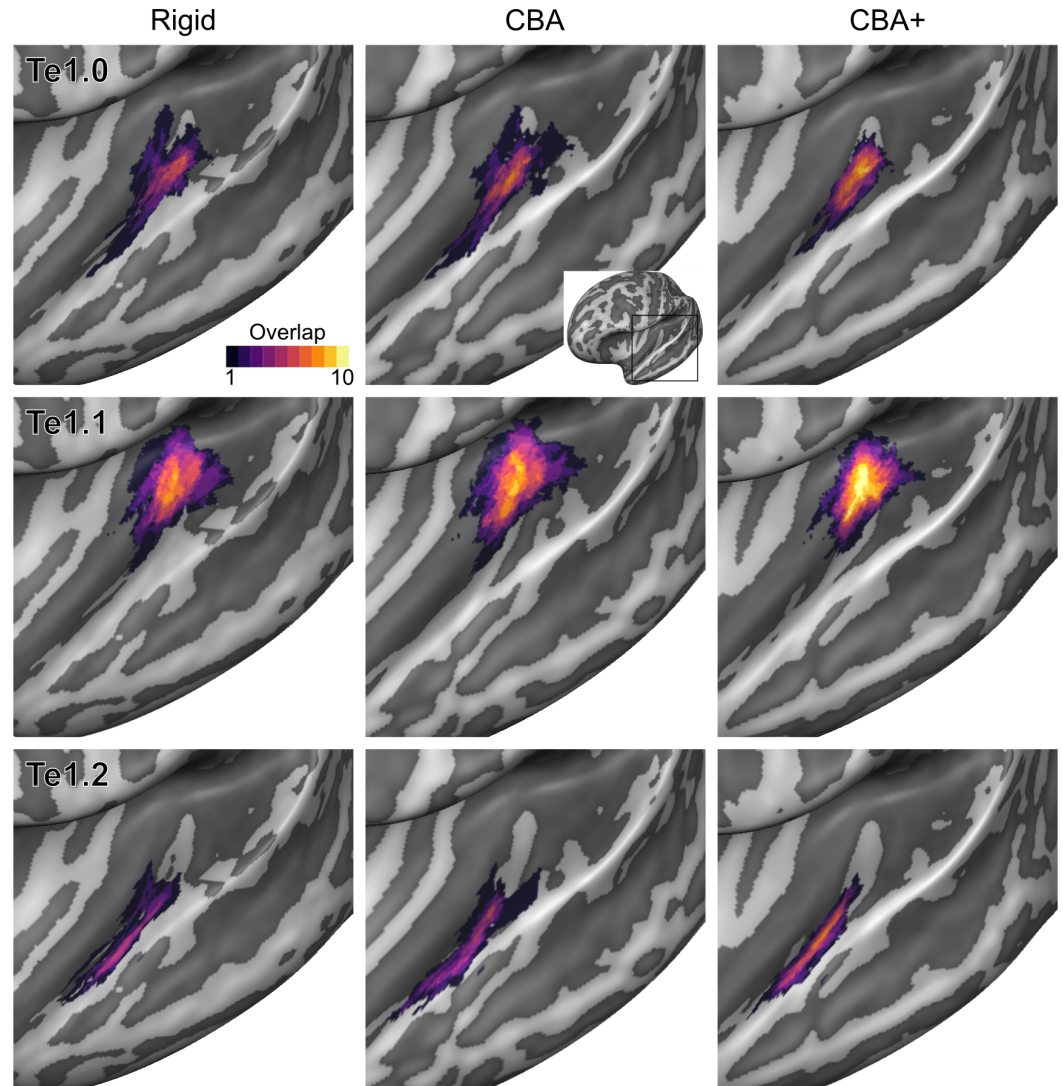


Figure 2. Probabilistic maps (after alignment) indicating the number of subjects for which a given vertex is labelled as belonging to the cyto-architectonic areas Te1.0, Te1.1 and Te1.2 are presented on inflated group average cortical surfaces of the left hemisphere. Columns show spherical rigid body alignment, curvature based alignment (CBA) and curvature based alignment with anatomical priors (CBA+) from left to right. Improvements in the micro-anatomical correspondence diminishes low values in the maps (purple) and increases the presence of high probability values (yellow).

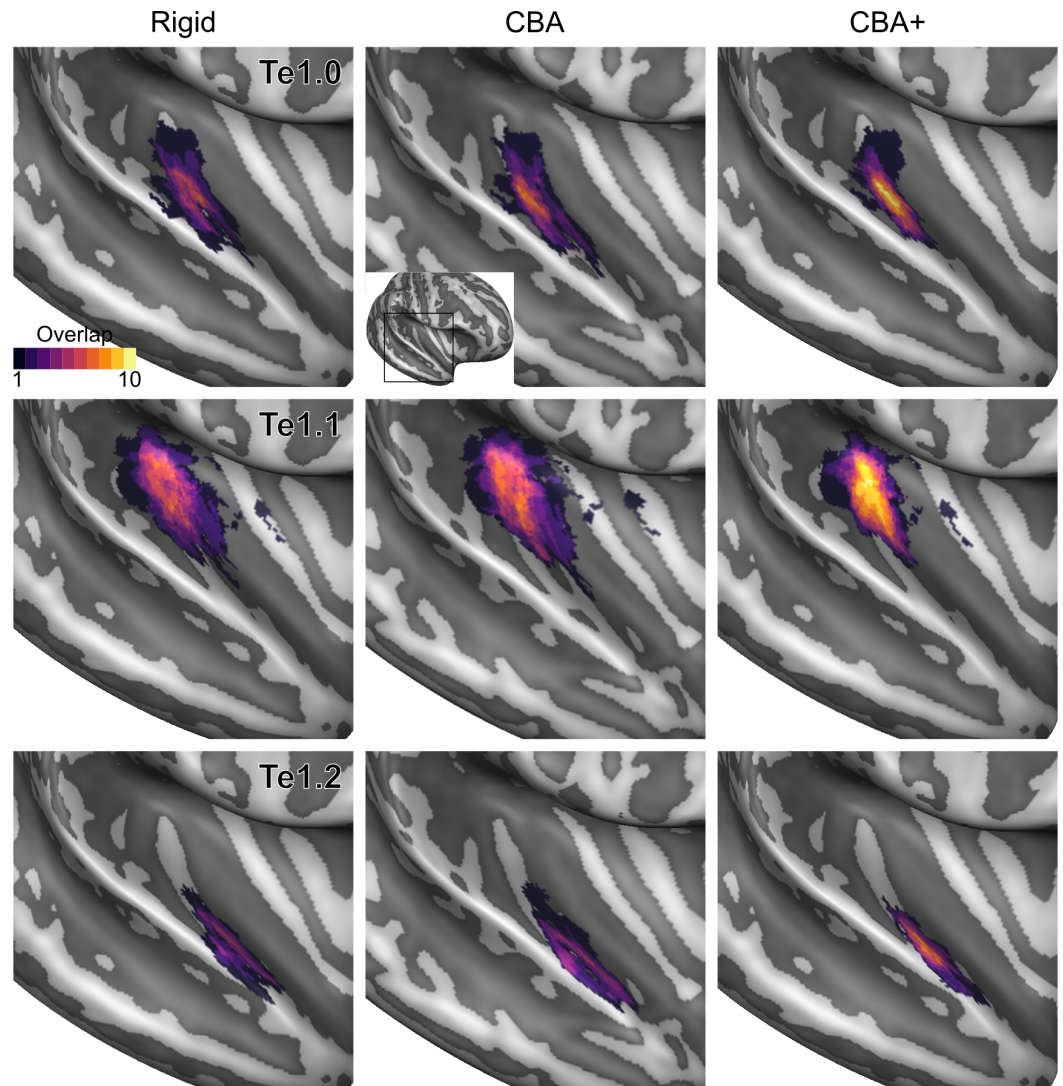


Figure 3. Probabilistic maps (after alignment) indicating the number of subjects for which a given vertex is labelled as belonging to the cyto-architectonic areas Te1.0, Te1.1 and Te1.2 are presented on inflated group average cortical surfaces of the right hemisphere. Columns show spherical rigid body alignment, curvature based alignment (CBA) and curvature based alignment with anatomical priors (CBA+) from left to right. Improvements in the micro-anatomical correspondence diminishes low values in the maps (purple) and increases the presence of high probability values (yellow).

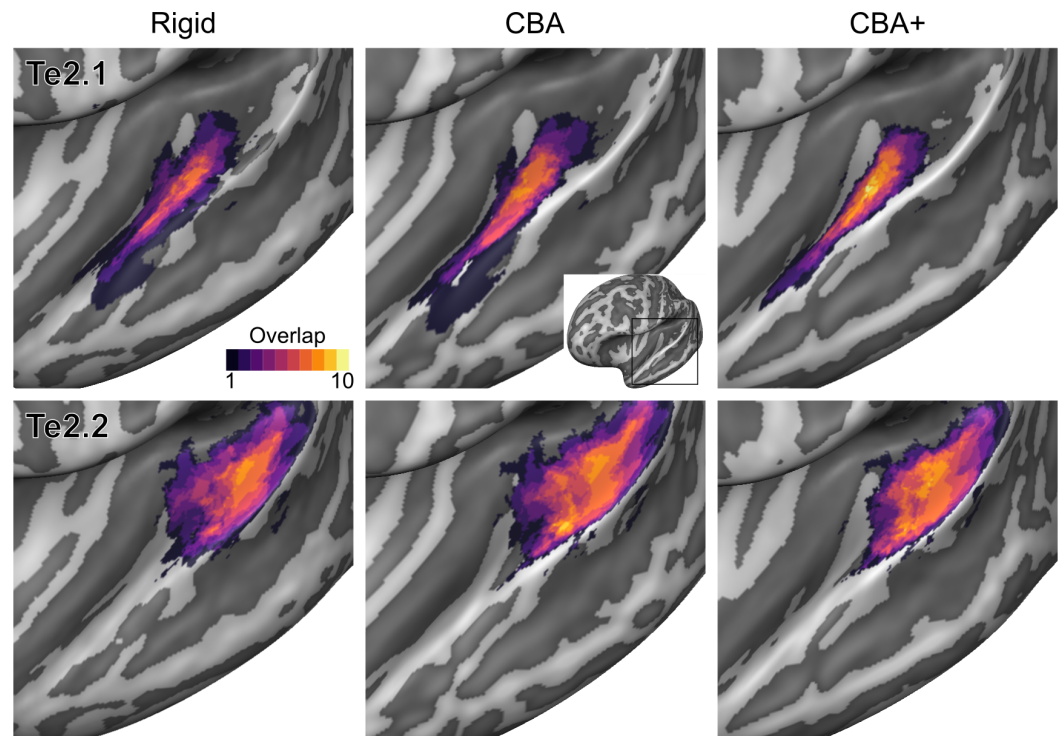


Figure 4. Probabilistic maps (after alignment) indicating the number of subjects for which a given vertex is labelled as belonging to the cyto-architectonic areas Te2.1 and Te2.2 are presented on inflated group average cortical surfaces of the left hemisphere. Columns show spherical rigid body alignment, curvature based alignment (CBA) and curvature based alignment with anatomical priors (CBA+) from left to right. Improvements the micro-anatomical correspondence diminishes low values in the maps (purple) and increases the presence of high probability values (yellow).

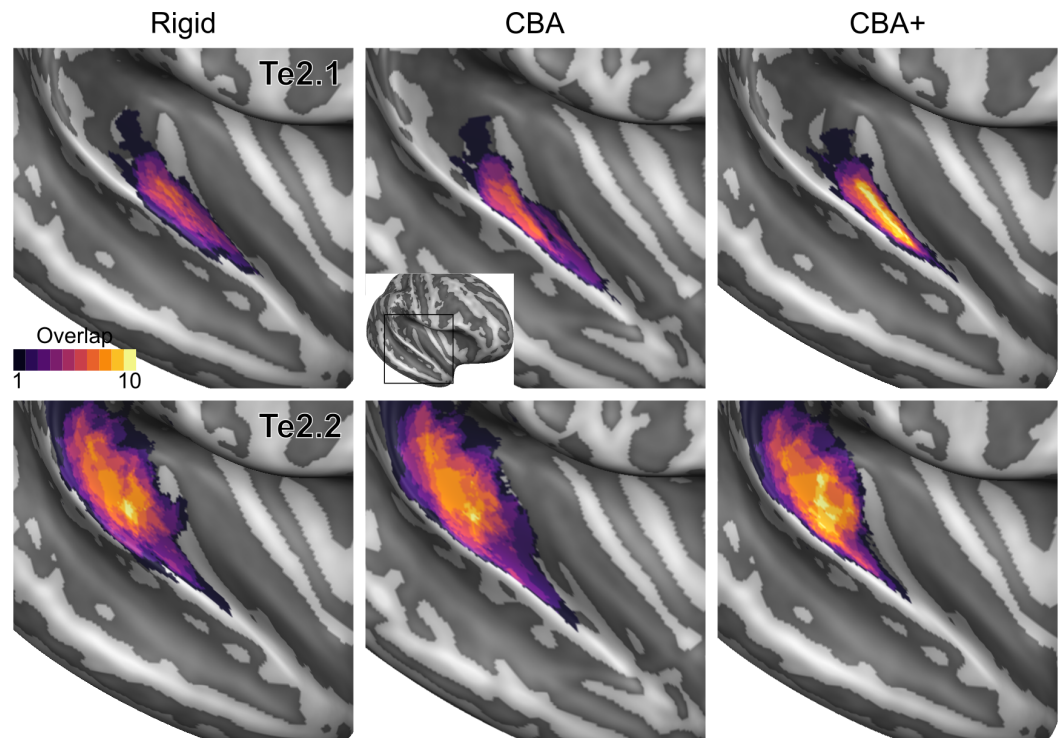


Figure 5. Probabilistic maps (after alignment) indicating the number of subjects for which a given vertex is labelled as belonging to the cyto-architectonic areas Te2.1 and Te2.2 are presented on inflated group average cortical surfaces of the right hemisphere. Columns show spherical rigid body alignment, curvature based alignment (CBA) and curvature based alignment with anatomical priors (CBA+) from left to right. Improvements in the micro-anatomical correspondence diminishes low values in the maps (purple) and increases the presence of high probability values (yellow).

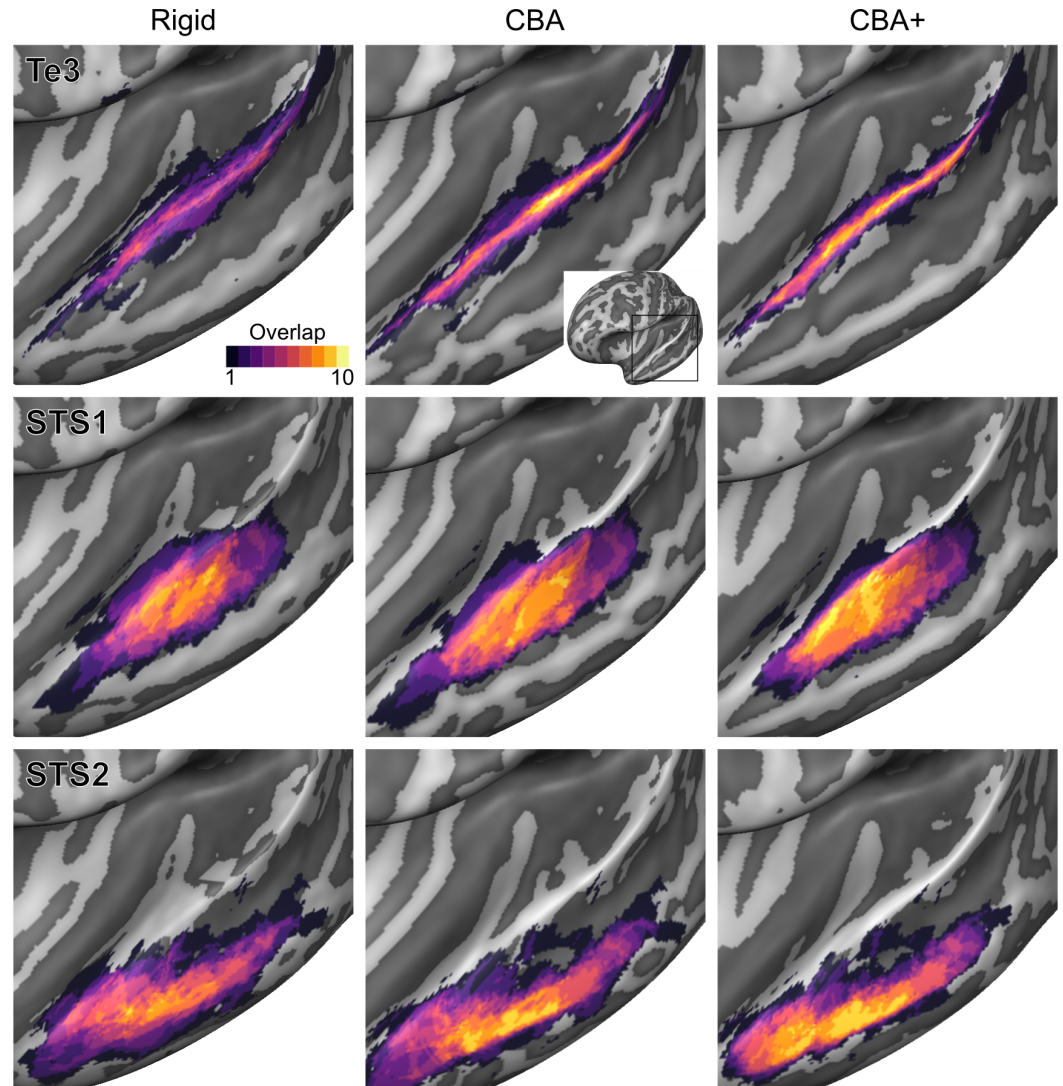


Figure 6. Probabilistic maps (after alignment) indicating the number of subjects for which a given vertex is labelled as belonging to the cyto-architectonic areas Te3, STS1 and STS2 are presented on inflated group average cortical surfaces of the left hemisphere. Columns show spherical rigid body alignment, curvature based alignment (CBA) and curvature based alignment with anatomical priors (CBA+) from left to right. Improvements in the micro-anatomical correspondence diminishes low values in the maps (purple) and increases the presence of high probability values (yellow).

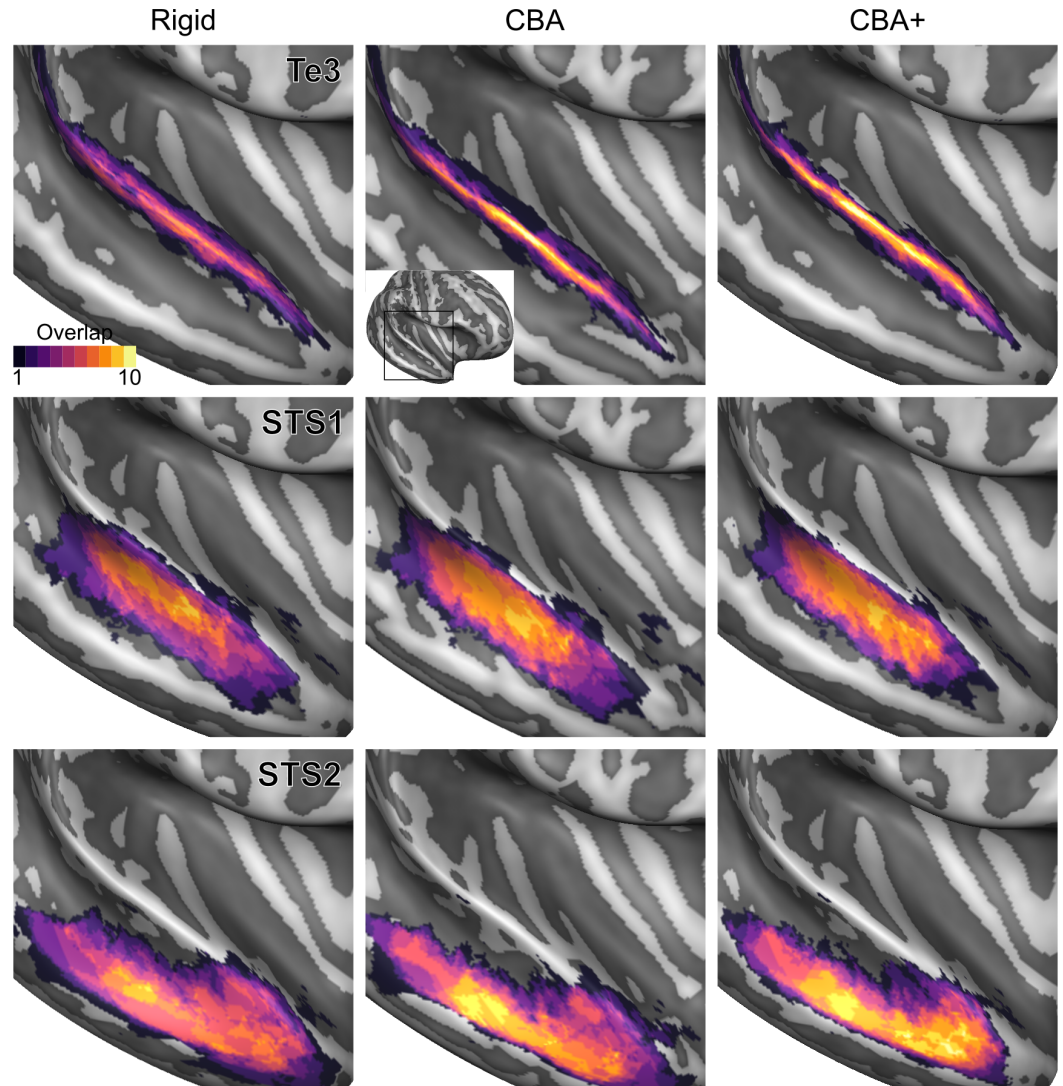


Figure 7. Probabilistic maps (after alignment) indicating the number of subjects for which a given vertex is labelled as belonging to the cyto-architectonic areas Te3, STS1 and STS2 are presented on inflated group average cortical surfaces of the right hemisphere. Columns show spherical rigid body alignment, curvature based alignment (CBA) and curvature based alignment with anatomical priors (CBA+) from left to right. Improvements in the micro-anatomical correspondence diminishes low values in the maps (purple) and increases the presence of high probability values (yellow).

Left hemisphere

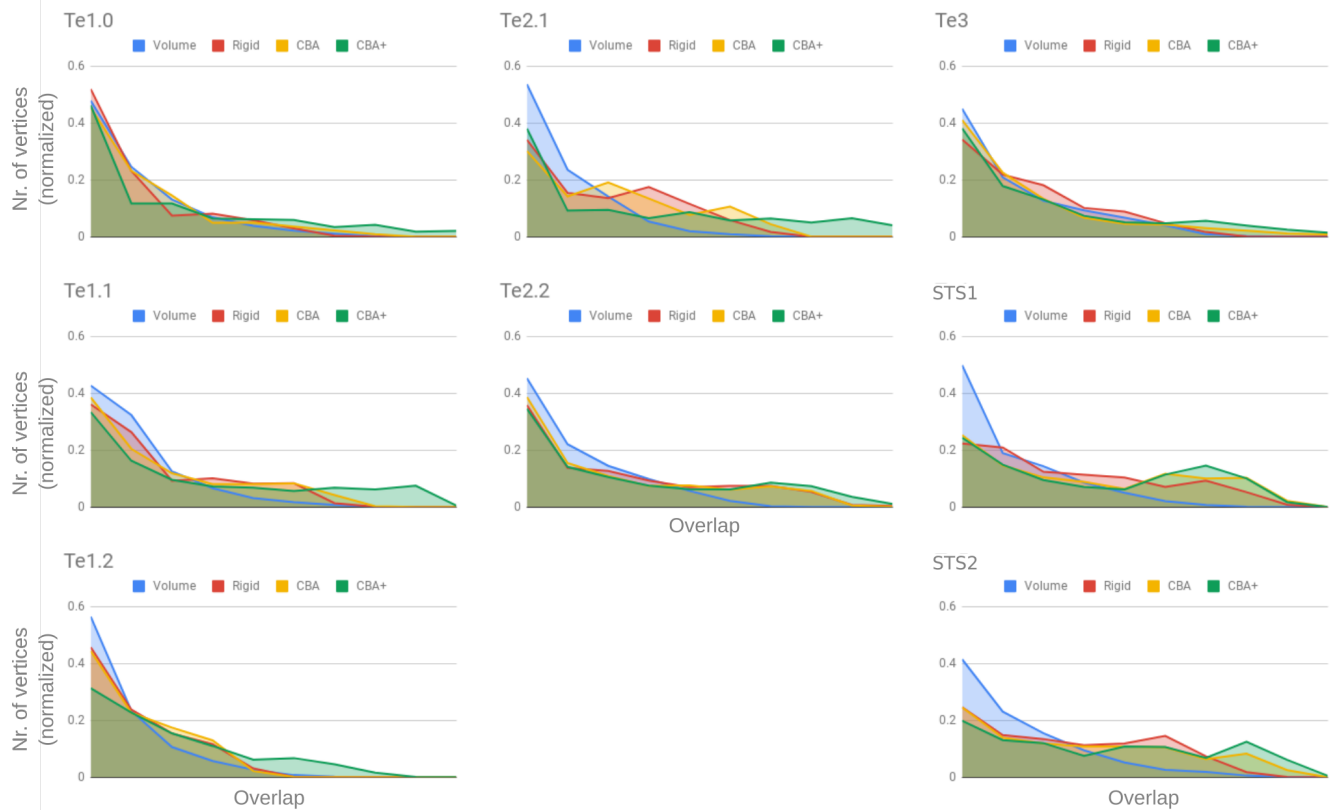


Figure 8. Histograms of the overlap across cyto-architectonic areas in the left hemisphere. The histograms are normalized by the number of vertices per area. The x-axis represents the probability value (an overlap from 1 out of ten [left] to 10 out of 10 participants [right]). The ideal co-registration method should show a less left skewed distribution. It can be seen that CBA+ shows the lowest skew towards the left in comparison to other methods.

Right hemisphere

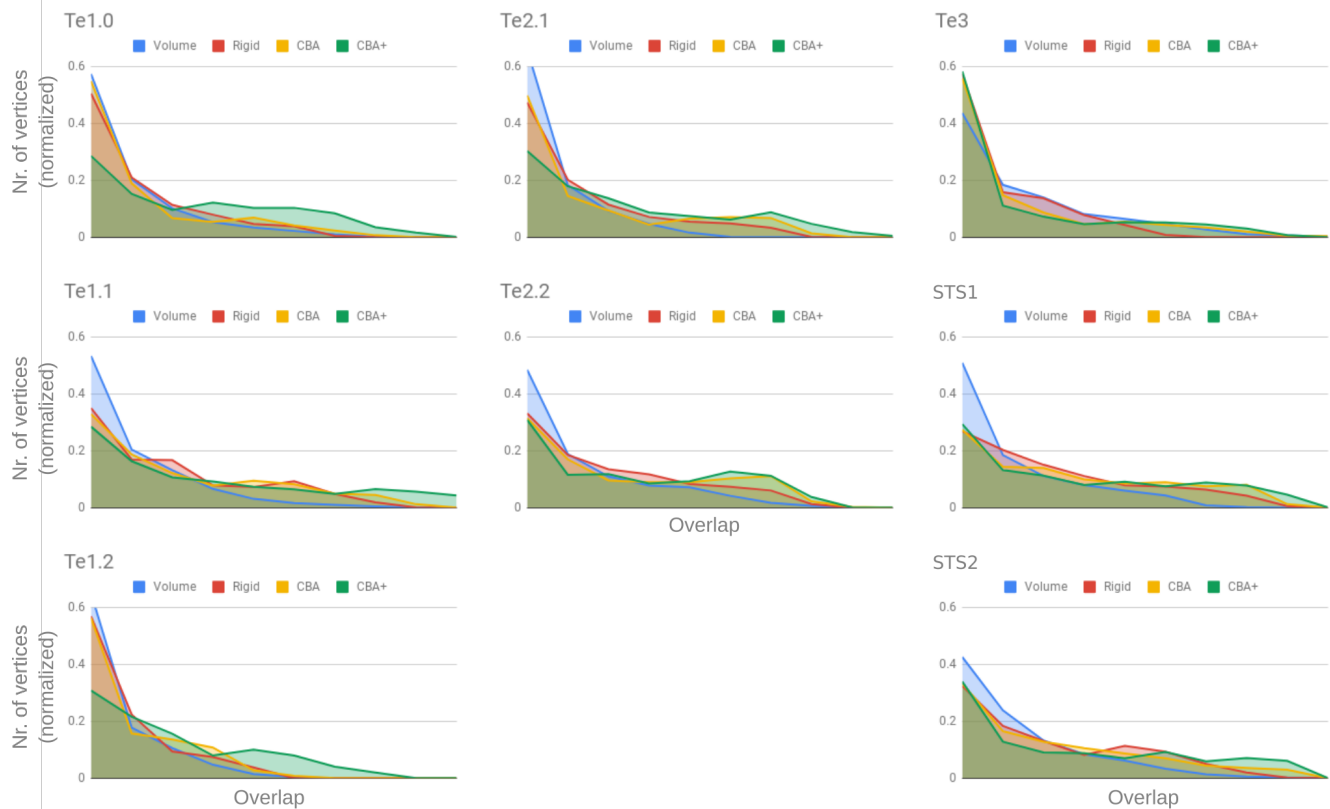


Figure 9. Histograms of the overlap across cyto-architectonic areas in the right hemisphere. The histograms are normalized by the number of vertices per area. The x-axis represents the probability value (an overlap from 1 out of ten [left] to 10 out of 10 participants [right]). The ideal co-registration method should show less left skewed distribution. It can be seen that CBA+ shows the lowest skew towards the left in comparison to other methods.

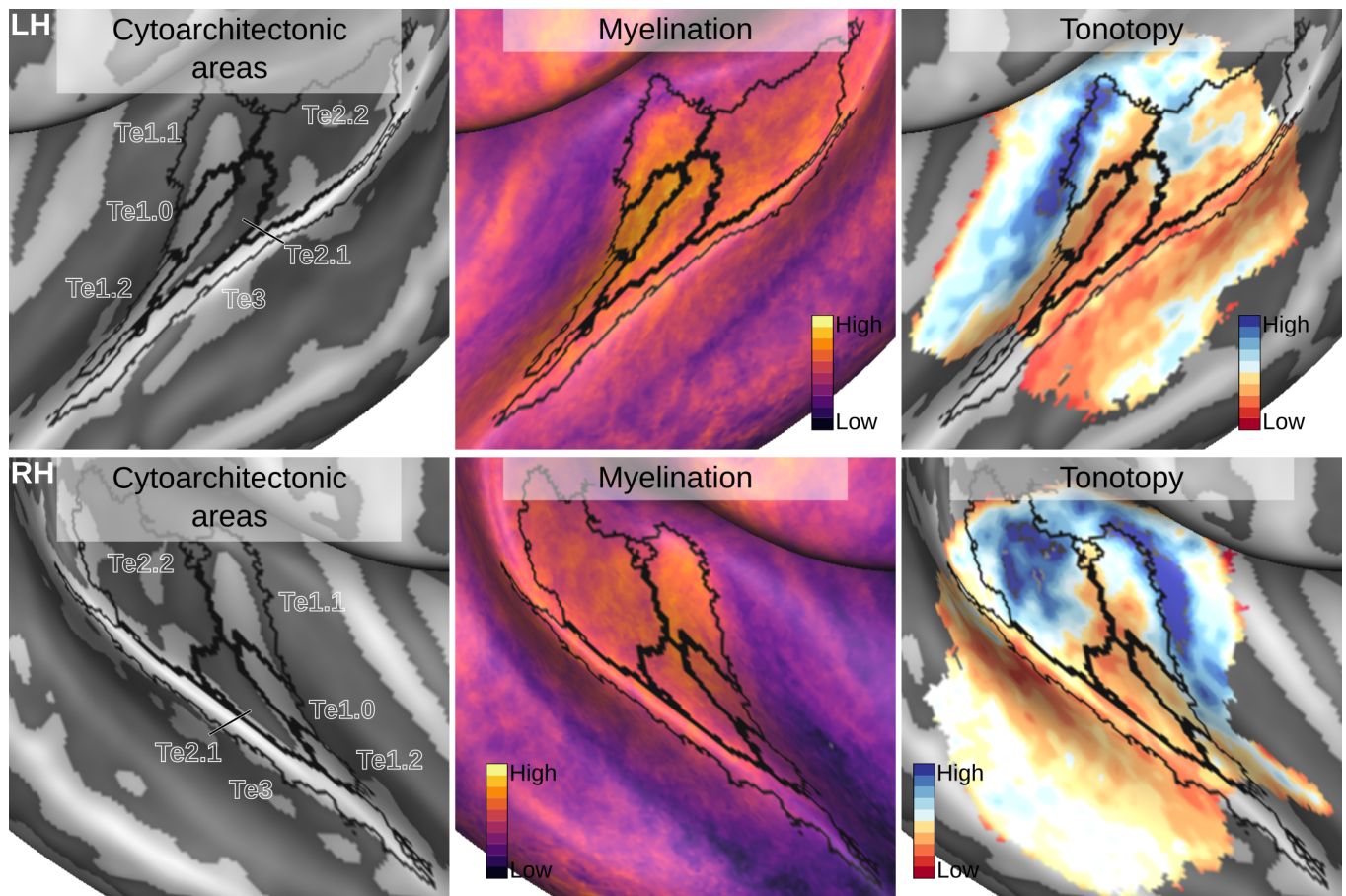


Figure 10. Relation between in vivo MRI measures and the cyto-architectonic atlas. The cyto-architectonic areas are delineated with black lines. The myelination index is computed from the division of T_1w and T_2^*w data. Tonotopy reflects the voxel-wise frequency preference estimated with fMRI encoding from the response to natural sound stimuli. All measures are sampled on the middle gray matter surfaces.

Figure 10-Figure supplement 1. The same maps projected to an in vivo multi-modal MRI group atlas (Glasser et al., 2016).

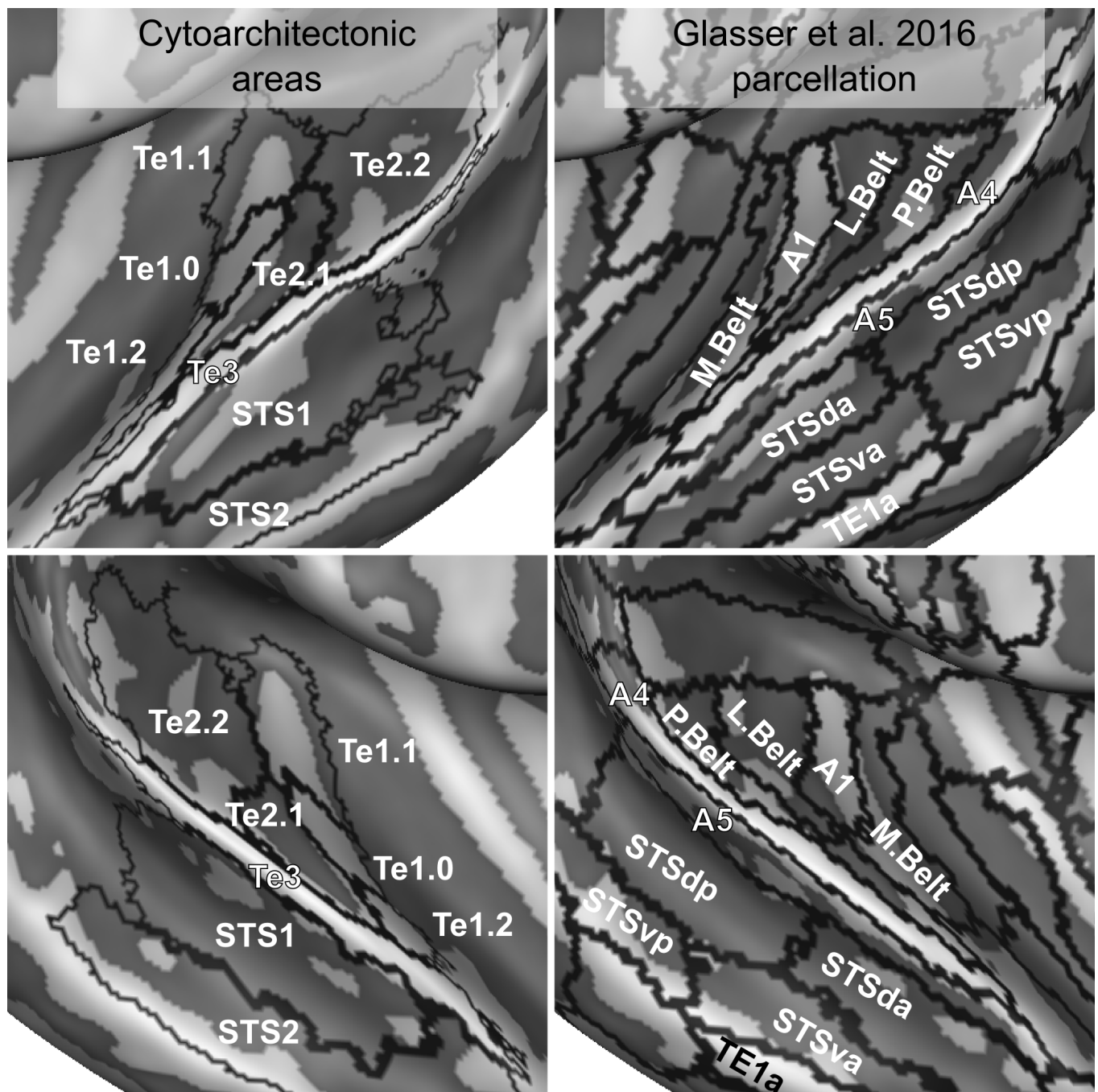


Figure 11. Comparison of cyto-architectonic areas *Morosan et al. (2001, 2005)* and multi modal MRI based labels (*Glasser et al., 2016*). Areas on Heschl's Gyrus differ between the two atlases.

Discussion

188
189 The superior temporal plane shows considerable macro-anatomical variability across individu-
190 als (*Pfeifer, 1921, 1936; Von Economo and Horn, 1930; Rademacher et al., 1993; Zoellner et al.,*
191 *2019*). Here we evaluated the effect of macro-anatomical variability on localizing cyto-architectonic
192 areas across different brains. We have used ten individual brains available from the JuBrain cyto-
193 architectonic Atlas¹ (*Amunts and Zilles, 2015*) together with a surface registration method that
194 minimizes macro-anatomical variability around the transverse temporal gyrus (similar to *Rosenke*
195 *et al., 2018*) to show that minimizing macro-anatomical variability in the superior temporal plane
196 results in improved micro-anatomical correspondence across brains.

197 Applying a surface registration for inter-subject alignment required accurate segmentation of
198 the post mortem MRI dataset. While this issue has been tackled before for the investigation of
199 cyto-architectonic areas in the visual cortex *Rosenke et al. (2018)*, an accurate segmentation of
200 the temporal areas was not available. To obtain such segmentation and reduce the amount of
201 manual corrections, we have used a tailored procedure based on image filtering and histogram
202 based segmentation (*Gulban et al., 2018b*). The resulting segmentations allowed us to define the
203 macro-anatomical variability in the sample (see *Figure 13*). The available ten brains showed typical
204 variations in the morphology of the Heschl's Gyrus (with a single Heschl's Gyrus being the most
205 prevalent one), as well as cases in which the Heschl's Gyrus was continuous to the anterior portion
206 of the superior temporal gyrus (*Heschl, 1878*).

207 The segmented hemispheres were used for cortex based alignment. The standard approach
208 minimizes macro-anatomical variation across subjects (i.e. maximizes the overlap of the curvature
209 maps) across the whole brain (in a coarse to fine iterative approach). As such, standard CBA is
210 driven by the major anatomical landmarks including the superior temporal gyrus and sulcus. This,
211 however, can result in compromised alignment of smaller (but consistent) anatomical features
212 such as the Heschl's Gyrus. This can be seen in *Figure 1* (middle column) where the compromised
213 alignment of the Heschl's Gyrus across hemispheres is indicated by the reduced sharpness of the
214 averaged binarized curvature maps. For this reason, here we have considered the application of an
215 approach tailored to the superior temporal plane. By providing additional landmarks (the Heschl's
216 Gyrus, the superior temporal gyrus/sulcus and middle temporal gyrus) to the CBA procedure, we
217 improved the alignment across subjects in the superior temporal cortex (see e.g. the difference
218 in the average curvature maps between standard CBA and CBA+ in *Figure 1*). Both the CBA and
219 CBA+ approach greatly improved the macro-anatomical correspondence when compared to a rigid
220 body procedure (which by sampling the volumetric data on surfaces already offers an improvement
221 compared to the original volumetric alignment - see *Figure 8* and *Figure 9*). The advantage for the
222 tailored approach (CBA+, rightmost column in *Figure 1*) is stronger on the right hemisphere, with
223 some residual misalignment for the left Heschl's Gyrus. This difference in performance could be
224 explained by the larger prevalence (within our sample) in the left hemisphere of cases with the
225 Heschl's Gyrus merging with the anterior portion of the superior temporal gyrus (i.e. split superior
226 temporal gyrus cases; two in the left and one in the right hemisphere). In the future, a larger sample
227 could allow evaluating this issue, as well as the impact that the inclusion of this macro-anatomical
228 variation has on the alignment of regions close to the superior temporal gyrus, by evaluating the
229 alignment separately (with and without) such cases.

230 Improving macro-anatomical correspondence resulted in improved overlap of the cyto-architectonic
231 areas across subjects. As a result of the CBA+ alignment, the micro-anatomically defined areas
232 were smaller and the probability for a vertex to be labelled as belonging to the same area across
233 the post mortem samples was higher (see Figures 2-7 and the histograms in *Figure 8* and *Fig-*
234 *ure 9*). The tailored approach (CBA+) resulted in increased overlap (also compared to standard
235 CBA) in all areas but especially for those on Heschl's Gyrus or immediately adjacent to it (Te1.0,
236 Te1.1, Te1.2 and Te2.1). This result is a direct consequence of defining the (most anterior) Heschl's

¹The JuBrain atlas is available through the Atlas of the Human Brain Project <https://jubrain.fz-juelich.de/>

237 Gyrus as an additional landmark for alignment. The most anterior Heschl's Gyrus was recognized
238 as the putative location of primary auditory cortex in the case of complete duplication on the
239 basis of myelo-architecture (*Hackett et al., 2001*). When this anatomical landmark is not used,
240 the duplication of the Heschl's gyrus results in poorer matching across subjects (i.e., the most
241 posterior duplication of some subjects is aligned to the single Heschl's Gyrus of other subjects).
242 The post mortem dataset includes six Heschl's Gyrus duplication cases (four in the right and two
243 in the left hemisphere). Follow up studies are needed to evaluate the effect of an incomplete
244 duplication of Heschl's Gyrus. As previous myelo-architecture studies reported a shift of primary
245 areas towards the intermediate Heschl's sulcus in the case of an incomplete duplication (*Hackett*
246 *et al., 2001*), a partial alignment of the primary areas (Te1.0 and Te1.1) may be expected. Exam-
247 ining the effect of an incomplete duplication on micro-anatomical alignment provide additional
248 insights for a further refinement of the alignment procedure we propose here. In addition to the
249 anterior Heschl's Gyrus, CBA+ includes the superior temporal gyrus/sulcus and middle tempo-
250 ral gyrus as anatomical landmarks. While to a lesser degree than the areas on Heschl's Gyrus,
251 areas along these landmarks were also better realigned by CBA+. This indicates that favoring
252 these gyri/sulci with respect to other major landmarks on the cortex is beneficial for the align-
253 ment of temporal areas. The improved cyto-architectonic overlap obtained with CBA+ suggests
254 that this approach may be relevant for the functional and anatomical investigation of (auditory)
255 temporal areas in vivo, as well as the investigation (post mortem and in vivo) of other cortical
256 regions in which macro anatomical variability is high. We make the individual hemisphere sur-
257 face models and the individual cyto-architectonic areas used in this study publicly available at
258 <https://kg.ebrains.eu/search/instances/Dataset/ff71a4d1-ea14-4ed6-898e-b92d95b3c446>.

259 To showcase the application of CBA+ to the analysis of in vivo MRI data, we applied the same
260 procedure to align anatomical and functional data collected at 7 Tesla across individuals. In addition,
261 we used CBA+ to align the in vivo data to the improved cyto-architectonic atlas.

262 The pattern of myelin related intra-cortical contrast followed previous reports (*Glasser and*
263 *Van Essen, 2011; Dick et al., 2012; De Martino et al., 2015*). The alignment to the cyto-architectonic
264 atlas shows a high myelin related contrast in area Te1.0, in agreement with previous studies (*Dick*
265 *et al., 2012*). Myelin related contrast was high also in the most medial portion of Heschl's Gyrus
266 (Te1.1) and decreased when moving away from Heschl's Gyrus. While subtle differences between
267 Te1.0 and Te1.1 were already noticeable, a more clear cut separation between these regions may
268 require the evaluation of myelin related contrast across depths similarly to previous approaches
269 (*Dick et al., 2012; De Martino et al., 2015*). In addition, future investigations may evaluate the
270 information provided by intra anatomical contrast resulting from in vivo MRI acquisitions other
271 than the one we considered here. For instance using the orientation of intra cortical fibres (*McNab*
272 *et al., 2013; Gulban et al., 2018a*).

273 The group tonotopy maps we derived from the in vivo data follow previous reports (*Dick et al.,*
274 *2012; Moerel et al., 2014; Besle et al., 2018*). In particular, they show one gradient within area Te1.1
275 progressing from high to low frequencies in antero-medial to postero-lateral direction. Based on the
276 average maps, a full tonotopic gradient was not visible in Te1.0, which was corresponding mainly
277 with the low frequency area in medial Heschl's Gyrus. This pattern may be the result of excessive
278 smoothing caused by inter-subject averaging that highlights the larger frequency gradient that in
279 tonotopic maps progresses in the anterior-posterior direction on the planum temporale and thus
280 favors the interpretation of the pattern within larger cortical areas (*Moerel et al., 2014*). More fine
281 grained information (within smaller areas such as e.g. Te1.0) could be leveraged by considering
282 single subjects in the future (*Moerel et al., 2014*). Te2.2 captured the most posterior portion of
283 the larger tonotopic gradient that, consistently with previous reports, we identify as running in
284 a direction orthogonal to Heschl's Gyrus (*Moerel et al., 2014; Besle et al., 2018*). The other cyto-
285 architectonic regions that overlapped with our functional acquisition field of view (Te2.1 and Te3)
286 covered low frequency preferring regions of the tonotopic map in the lateral portion of the Heschl's
287 sulcus and the superior temporal gyrus. These results argue for the necessity of interpreting large

288 scale tonotopic maps which alone do not allow defining the borders between cortical areas (*Moerel*
289 *et al., 2014*). A large tonotopic gradient unarguably runs in a posterior to anterior direction *Da Costa*
290 *et al. (2011); Besle et al. (2018)*. Equating this gradient with the gradient that identifies the primary
291 auditory cortex results in a view in which the core lies orthogonal to Heschl's Gyrus (*Da Costa et al.,*
292 *2011; Saenz and Langers, 2014; Besle et al., 2018*). On the other hand, the cyto-architectonic areas
293 -now restricted in size by better aligning macro-anatomy- suggest that the auditory core (Te1) runs
294 along Heschl's Gyrus (i.e. the "classical" view; (*Dick et al., 2012; Moerel et al., 2014*)). This view is
295 strengthened by the combined interpretation of myelin and tonotopy (see *Figure 10* and results in
296 (*Dick et al., 2012; Moerel et al., 2014*)) as well as other auditory cortical functional characteristics
297 (e.g., frequency selectivity; (*Moerel et al., 2014*)).

298 Interesting differences exist between the surface projection of the cyto-architectonic areas
299 compared to a recent parcellation of the temporal lobe derived solely from in vivo imaging (*Glasser*
300 *et al. (2016)* - see *Figure 11*). Cyto-architectonic areas Te1.1, Te1.0 and Te1.2 lie postero-medial to
301 antero-lateral along the Heschl's Gyrus. The most lateral subdivision (Te1.2) has been suggested to
302 be the human homologue of area RT in the monkey (and thus part of the auditory core) or part
303 of the lateral belt (*Moerel et al., 2014*). In the multi modal MRI parcellation, on the other hand,
304 Heschl's Gyrus is divided in an area labelled as A1, corresponding to the most medial two thirds, and
305 its most lateral portion, which is part of the area labelled as the medial belt. Outside of the Heschl's
306 Gyrus other differences between the in vivo and post mortem atlas are visible. The lateral belt and
307 parabelt areas as defined in the in vivo atlas occupy an area roughly corresponding to Te2, but the
308 border between the areas labelled as belt and parabelt run approximately orthogonal to the border
309 between Te2.1 and Te2.2. Te3, previously considered as an homologue of parabelt, corresponds to
310 the areas labelled as A4 and A5 in the in vivo atlas. STS1 overlaps with the dorsal portion of superior
311 temporal sulcus (STSda and STSdp in the in vivo atlas) and STS2 with the ventral portion of superior
312 temporal sulcus for the most part. While the in vivo multi modal atlas has been derived from a
313 large sample of participants (N=210), these differences may be caused by an insufficient amount of
314 information available in the in vivo data used for the parcellation of the superior temporal plane.

315 In conclusion, here we show that an alignment procedure tailored to the superior temporal
316 cortex and driven by anatomical priors together with curvature values improves inter-subject
317 correspondence of cyto-architectonic areas. Reducing macro-anatomical variability and improving
318 cyto-architectural correspondence may reduce the inter-subject variability of (anatomical and
319 functional) characteristics probed in vivo, resulting in a more accurate definition of putative cortical
320 (temporal) areas. Thereby our tailored approach has the potential to improve the investigation
321 of anatomical and functional characteristics of auditory cortical areas using in vivo MRI. While we
322 demonstrate its effectiveness in the temporal cortex, this approach is easily extendable to other
323 cortical areas in which macro-anatomical inter subject variability is not easily accounted for by
324 standard surface registration methods. Future studies should evaluate if this procedure, apart
325 from being more accurate, is equally accurate for all known macro-anatomical variations of the
326 morphology of the Heschl's Gyrus. To demonstrate its applicability in vivo, we used CBA+ on data
327 collected at 7 Tesla and coregistered our data to the post mortem atlas. In future work, CBA+ may
328 aid the parcellation of the auditory cortex based as well as the other brain regions (e.g. frontal
329 cortex) on in vivo data.

330 **Methods**

331 **Post mortem data**

332 We used the cyto-architectonically labeled temporal cortical areas of the ten brains used in *Morosan*
333 *et al. (2001, 2005); Zachlod et al. (2020)*. The labeled areas were Te1.0, Te1.1, Te1.2, Te2.1, Te2.2
334 (*Morosan et al., 2001*), Te3 (*Morosan et al., 2005*), STS1, STS2 (*Zachlod et al., 2020*). All brains were
335 linearly registered to Colin27 space (*Evans et al., 2012*) at 1 mm isotropic resolution, which was the
336 starting point for all further analyses.

337 Cortical segmentation

338 In order to perform cortex based alignment, the white matter - gray matter boundary was seg-
339 mented in all ten post mortem brains. The anatomical image quality was insufficient to employ
340 fully automatic segmentation methods. To mitigate this issue, we employed a spatial filter that was
341 applied to an upsampled version of the data (to 0.5mm isotropic). This spatial filter was tailored to
342 exploit the structure tensor field derived from the images. Our implementation of this procedure
343 -that mostly follows *Weickert (1998)*; *Mirebeau et al. (2015)*- included the following steps:

- 344 1. Smoothing the image for spatial regularization

$$\hat{v} = K_{\sigma} * v. \quad (1)$$

345 where $*$ indicates convolution and K is a Gaussian kernel with standard deviation defined by
346 σ . Here we have opted for $\sigma = 1$.

- 347 2. Computing the gradients of the image to obtain a vector field (we have used central differ-
348 ences)

$$\text{gradient}(\hat{v}) = \vec{v}. \quad (2)$$

- 349 3. Generating a structure tensor field by using the self outer product:

$$S = \vec{v} \cdot \vec{v}^T. \quad (3)$$

- 350 4. Decomposing (using eigen decomposition) the structure tensor field:

$$\text{eig}(S) \rightarrow \vec{e}_1, \vec{e}_2, \vec{e}_3 \text{ (eigen vectors) and } \lambda_1, \lambda_2, \lambda_3 \text{ (eigen values)}. \quad (4)$$

351 Note that the eigen vectors are sorted according to eigen values $\lambda_1 > \lambda_2 > \lambda_3$.

5. Using eigen values to derive a vector field:

$$\begin{aligned} \text{intensity} &= \lambda_1 + \lambda_2 + \lambda_3, \\ \text{range} &= (\lambda_1 - \lambda_3) / \text{intensity}, \\ w &= (|\text{range} - 0.5| + 0.5) - \text{intensity}. \end{aligned} \quad (5)$$

352 Here we wanted to enhance prolate ellipsoid tensors (also called surfels, surface elements,
353 $\lambda_1 \approx \lambda_2 > \lambda_3$) more than isotropic structure tensors ($\lambda_1 \approx \lambda_2 \approx \lambda_3$) and oblate ellipsoid tensor
354 (also called curvels, curve elements like tubes, $\lambda_1 > \lambda_2 \approx \lambda_3$).

- 355 6. Generating a diffusion tensor field from weighted eigen vectors:

$$(w \cdot e) = D. \quad (6)$$

- 356 7. Smoothing the diffusion tensor field.

$$\hat{D} = K_{\rho} * D \quad (7)$$

357 where $*$ indicates convolution and K is a 3D Gaussian kernel with σ standard deviation. Here
358 we have used $\rho = 1$. A higher value would enhance features at a larger spatial scale.

- 359 8. Computing a vector field (the flux field) using the diffusion tensor field and eigen vectors
360 (D_i is a tensor 3×3 ; \vec{v}_i is a vector 1×3):

$$\vec{f} = \hat{D} \cdot \vec{v}. \quad (8)$$

- 361 9. Updating the image (\vec{f}_i is a vector ; v_i is a scalar):

$$v_{\text{new}} = v + \text{divergence}(\vec{f}). \quad (9)$$

- 362 10. Repeating all steps until the desired number of iterations is reached (each iteration diffuses
363 the image more and the diffusion is non-linear and anisotropic).

364 For segmenting the post mortem data, here we iterated this process 40 times. This number
365 of iterations was visually judged as sufficient to enhance the boundary between white matter
366 and gray matter as well as distinguishing the two banks of sulci by rendering them sharper [see
367 *Figure 12*]. Our implementation is available within the Segmentator package version 1.5.3 (*Gulban
368 and Schneider, 2019*).

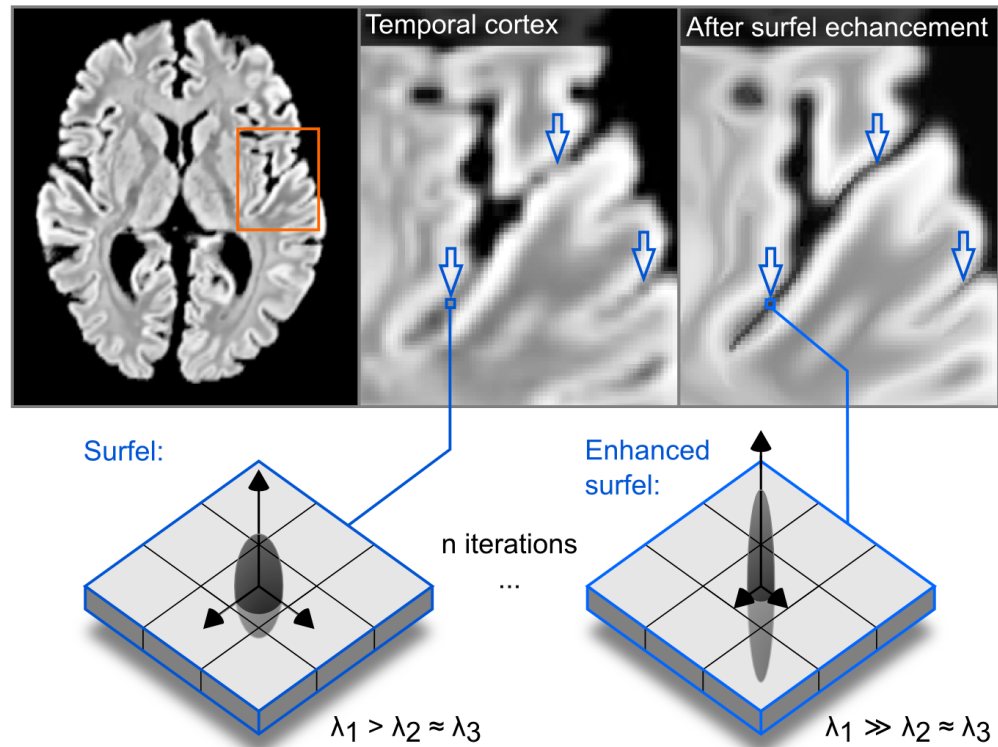


Figure 12. The effect of the structure enhancing filter shown on a transversal slice. Blue arrows point to locations where local contrast is sharpened.

369 Cortical surface reconstruction

370 After filtering the images, we generated an initial white matter segmentation using intensity-gradient
 371 magnitude joint 2D histograms (Gulban *et al.*, 2018b). This initial segmentation was corrected in two
 372 stages. First, manual corrections were performed by O.F.G using both enhanced and un-enhanced
 373 anatomical images (around 8 hours of manual work per brain). Second, after splitting left and right
 374 hemispheres, we generated surfaces as triangular meshes using the marching cubes method (as
 375 implemented in BrainVoyager 21.4, Goebel (2012)) and decimating the total amount of vertices to
 376 200000 (with approximately equal edge lengths). The surfaces were visually checked for bridges and
 377 holes and problematic areas were corrected until the Euler characteristic of each surface became
 378 2 (i.e. topologically identical to a sphere). **Figure 13** shows the morphological variation across the
 379 post mortem brains on the superior temporal cortex.

380 Cortical surface alignment

381 The prepared surfaces were inflated to an approximate sphere and mapped onto a high density
 382 spherical mesh (163842 vertices). Prior to cortex based alignment, the meshes were aligned using a
 383 spherical rigid body method to minimize curvature differences across subjects [see **Figure 1** left
 384 column]. Cortex based alignment was performed in two different ways. First, we non linearly
 385 registered the surfaces of each hemisphere across brains using standard cortex based alignment
 386 (i.e. minimizing curvature differences across individuals in a coarse to fine manner (Frost and
 387 Goebel, 2012)). Second, to tailor the alignment to the superior temporal cortices (left and right
 388 separately), we delineated four macro-anatomical landmarks: 1) the anterior Heschl's Gyrus; 2)
 389 the superior temporal gyrus; 3) the superior temporal sulcus and 3) the middle temporal gyrus
 390 (see **Figure 13** and **Figure 14**). These landmarks were used as additional information to determine
 391 the cost that is minimized during curvature based non-linear alignment in our tailored approach
 392 (i.e. CBA+). As for the standard surface alignment, CBA+ was performed across 4 spatial scales

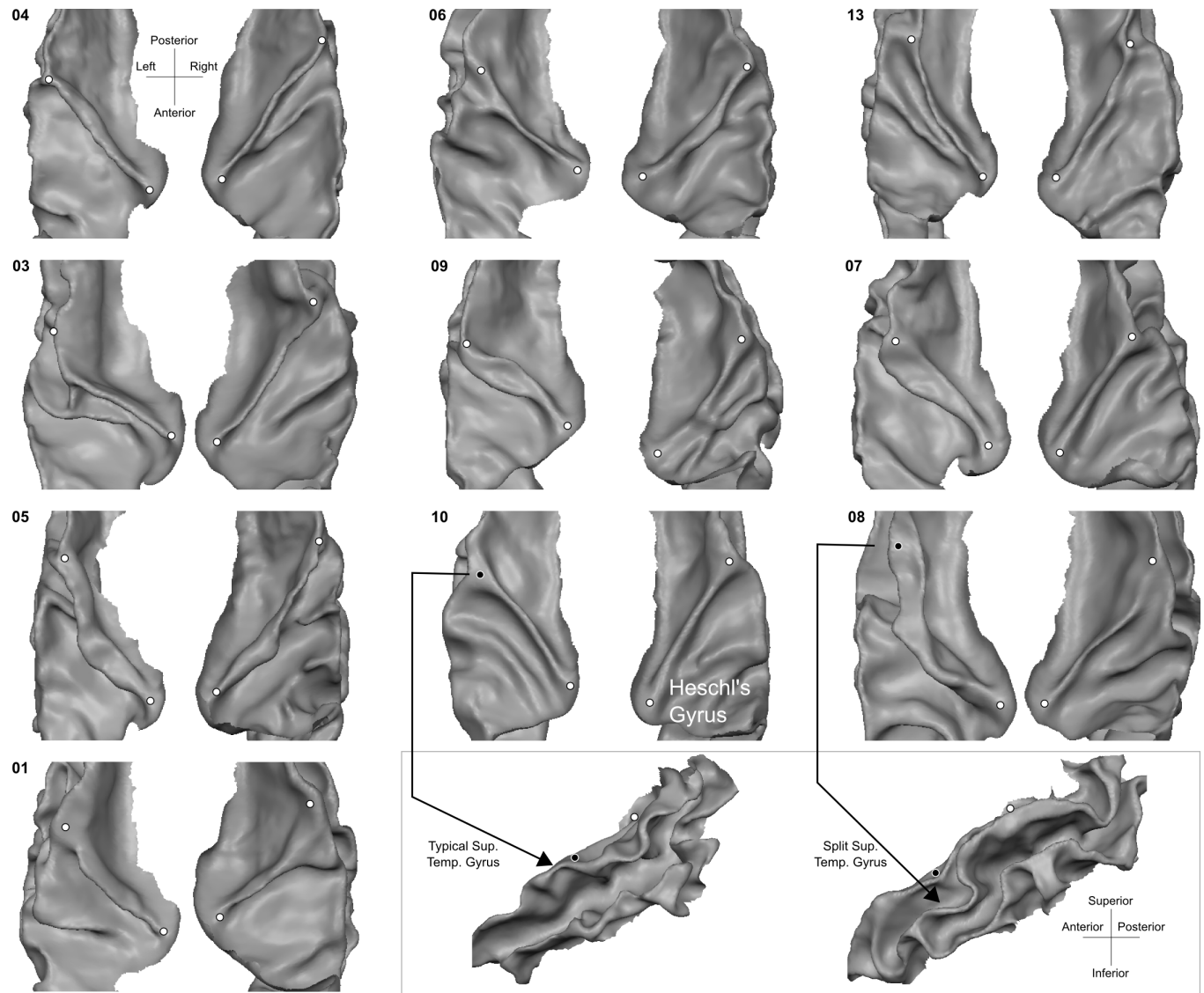
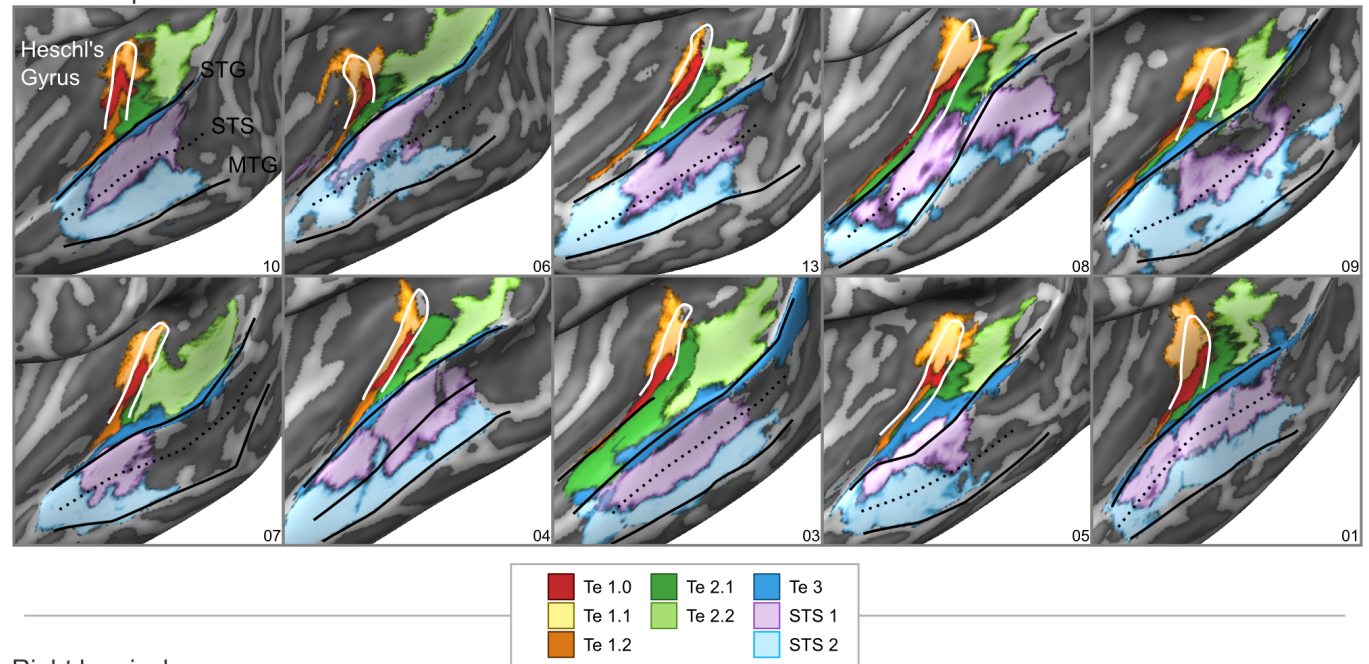


Figure 13. Individual superior temporal cortex white-gray matter boundary reconstructions. Anterior Heschl's Gyrus is indicated as the gyrus between white dots. The bottom right side shows the rare occurrence of a split superior temporal gyrus (*Heschl, 1878*) in contrast to a typical superior temporal gyrus from the side view.

Left hemisphere



Right hemisphere

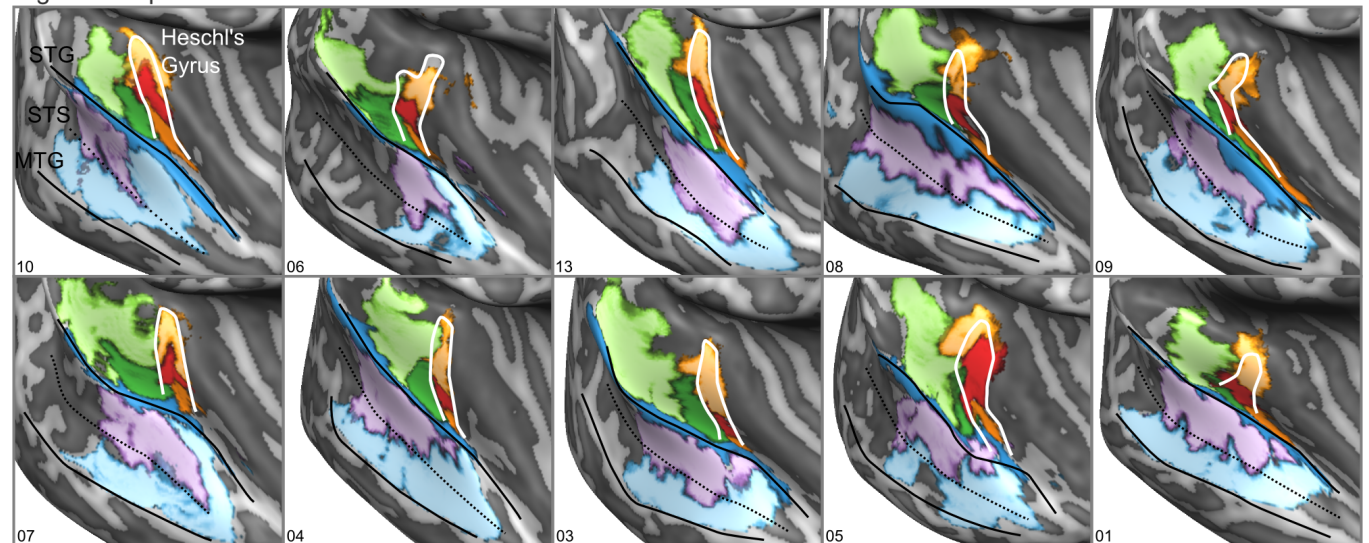


Figure 14. cyto-architectonic areas of *Morosan et al. (2001, 2005)*; *Zachlod et al. (2020)* sampled on the inflated cortical surfaces for each individual brain in the post mortem dataset. Anterior Heschl's Gyrus, superior temporal gyrus (STG), superior temporal sulcus (STS), and middle temporal gyrus (MTG) are indicated as line drawings.

393 (from very smooth to slightly smooth curvature maps) which is shown to improve curvature based
394 alignment overall (*Frost and Goebel, 2012; Tardif et al., 2015*). Both CBA and CBA+ were performed
395 using dynamic group averaging. The surface alignment yielded a mapping between each individual
396 to a group average brain, each consisting of the same number of vertices.

397 To evaluate the effect of alignment, we computed the overlap across individuals for each of the
398 cyto-architectonic areas. We compared our tailored alignment procedure to the original volumetric
399 Colin27 alignment (*Evans et al., 2012*), spherical rigid body alignment, and non-linear standard
400 cortex based alignment (see *Figure 14*).

401 **In vivo data**

402 **MRI acquisition**

403 We have used the dataset² described in (*Sitek et al., 2019*). This dataset includes: (I) T_1 weighted
404 (T_1w), proton density weighted (PDw) and T_2^* weighted (T_2^*w) anatomical images collected (using
405 a modified MPRAGE sequence) at a resolution of 0.7 mm isotropic (whole brain); (II) functional
406 images at collected at a resolution of 1.1 mm isotropic (partial coverage, coronal-oblique slab, multi
407 band factor=2; GRAPPA = 3) in response to the presentation of natural sounds (168 natural sounds;
408 24 runs divided in four cross validation splits of 18 training and 6 testing runs each (126 training
409 sounds and 42 testing sounds per split).

410 **Cortical segmentation and alignment**

411 Segmentations of both the white matter - gray matter interface and outer gray matter (also called
412 gray matter - cerebrospinal fluid interface) were done following BrainVoyager 2.8.4's advanced seg-
413 mentation pipeline (*Kemper et al., 2018*) and using the automatic bridge removal tool (*Kriegeskorte
414 and Goebel, 2001*). Manual corrections were done in ITK-SNAP (*Yushkevich et al., 2006*). All follow
415 up analyses were performed by sampling (anatomical and functional) data onto the middle gray
416 matter surfaces (defined using the equidistant methods (*Waehnert et al., 2014; Kemper et al.,
417 2018*) by the combination of inner and outer gray matter surfaces). This allowed us to minimize
418 partial voluming with white matter, cerebrospinal fluid or superficial vessels. These surfaces can be
419 seen for each individual in *Figure 15*.

420 The middle gray matter surfaces of all individuals were aligned using the procedure tailored to
421 the superior temporal plane described above (CBA+). The resulting group average mesh from the in
422 vivo dataset was aligned to the average post mortem mesh following the same procedure. This
423 allowed us to overlay probabilistic cyto-architectonic areas onto the in vivo group average cortical
424 surfaces and sample functional and anatomical data within each area.

425 **Myelination maps**

426 The processing steps followed to create myelination maps were similar to *De Martino et al. (2015)*.
427 T_1w images were divided by T_2^*w (T_1w/T_2^*w) and the resulting division image was masked by the
428 cortical gray matter segmentation. A histogram-based adaptive percentile threshold (based on
429 iterative deceleration of percentile differences) on the T_1w/T_2^*w image was used to discard voxels
430 with extreme intensities corresponding to vessels and regions in which the T_2^*w data were of
431 insufficient quality. Maps were rescaled to range between 0-100. This step was necessary to match
432 intensity ranges across subjects since we did not have quantitative measures. Values in the middle
433 gray matter of the rescaled maps were sampled onto the surface mesh.

434 **Tonotopy maps**

435 The functional data were preprocessed using BrainvoyagerQX v2.8.4 (*Goebel, 2012*). Slice-scan-
436 time correction, motion correction, temporal high-pass filtering (GLM-Fourier, 6 sines/cosines) and
437 temporal smoothing (Gaussian, kernel width of two acquisition volumes [i.e. 5.2 s]) were applied.
438 Default options in BrainvoyagerQX v2.8.4 were used aside from the explicitly stated values. The

²This dataset is available at: <https://openneuro.org/datasets/ds001942/versions/1.2.0>

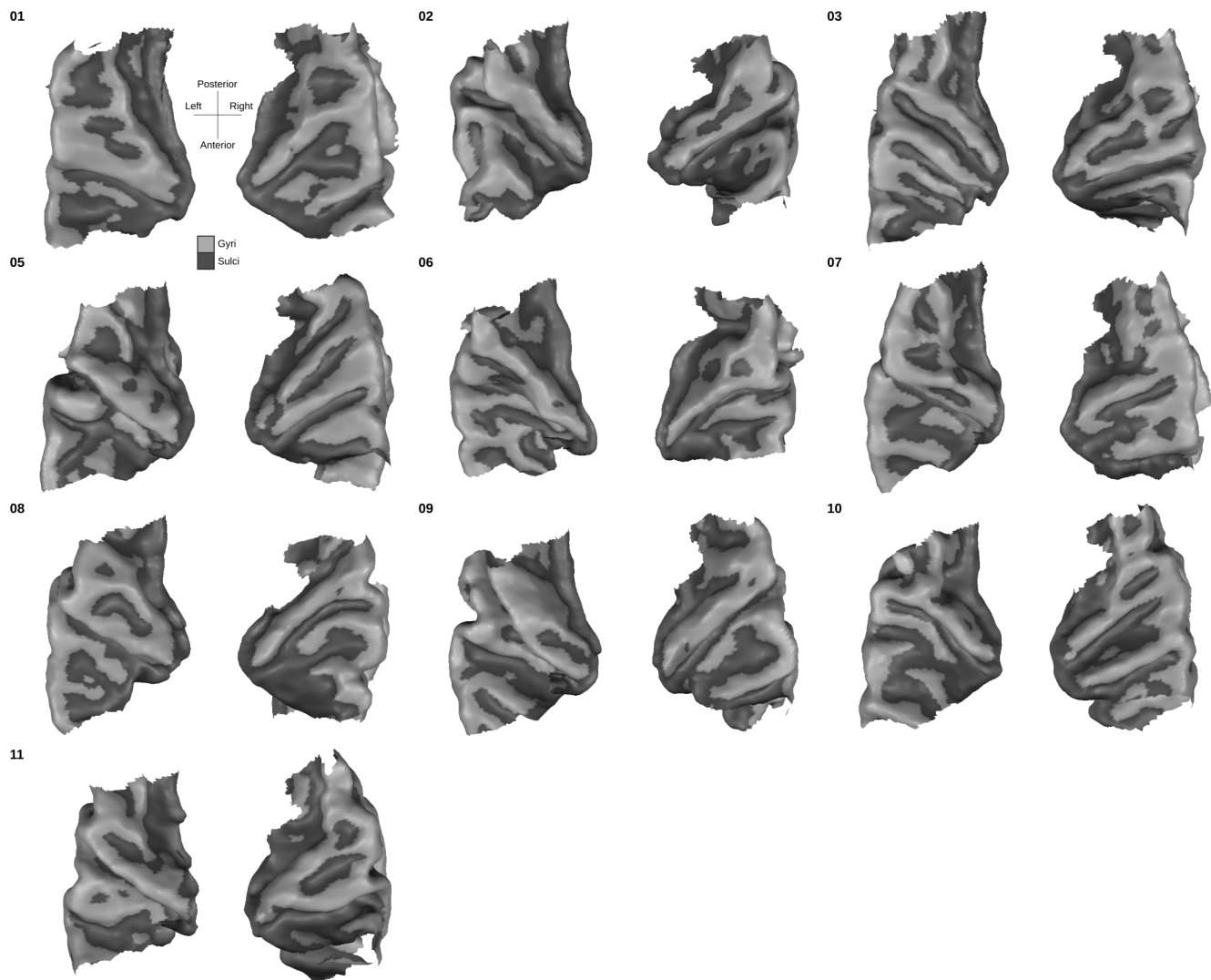


Figure 15. Individual superior temporal cortex middle-gray matter surface reconstructions from a bird's eye (top-down) view. Dark gray colored indicate sulci and light gray indicates gyri.

439 functional images were then distortion corrected using the opposite phase encoding direction
440 images using FSL-TOPUP (*Andersson et al., 2003*) as implemented in (*Smith et al., 2004*). The
441 conversion between Brainvoyager file types to NIfTI, which was required to perform distortion
442 correction, was done using Neuroelf version 1.1 (release candidate 2)³ in Matlab version 2016a.

443 After pre-processing, functional images were transformed to Talairach space using Brainvoy-
444 agerQX v2.8.4 at a resolution of 1 mm isotropic. We estimated the voxels' responses to each natural
445 sound in a two step procedure (*Moerel et al., 2013; Santoro et al., 2014*). First, the hemodynamic
446 response function (HRF) best characterizing the response of each voxel was obtained using a
447 deconvolution GLM (with 9 stick predictors together with the noise regressors) on the training
448 data (a subset of the functional runs). Second, the response to each natural sound (in training
449 and test set runs separately per cross validation) was estimated with using a GLM analysis and the
450 optimized HRF of each voxel. In addition to the predictors representing the experimental conditions
451 (i.e. the individual stimuli), the analysis included noise regressors obtained using GLM-denoise
452 (*Kay et al., 2013*). Note that the number of noise components and their spatial maps (allowing to
453 derive the temporal regressors) were estimated on the training data only (i.e. separately per each
454 cross-validation).

455 To estimate the voxels' preference to the acoustic content (i.e. sound frequencies) we fitted
456 (using Ridge Regression) the spectral sound representation obtained by passing the sounds through
457 a cochlear filter model (128 logarithmically spaced filters, see (*Chi et al., 2005; Moerel et al., 2013*))
458 to the voxels' responses (i.e. linearized encoding approach (*Kay et al., 2008*)). The frequency
459 associated with the largest linear weight after fitting defined the preference of each voxel (see
460 (*Moerel et al., 2012*) for more details on the procedure). Tonotopic maps were obtained by color
461 coding (red to blue) the frequency preference (low to high) at each voxel.

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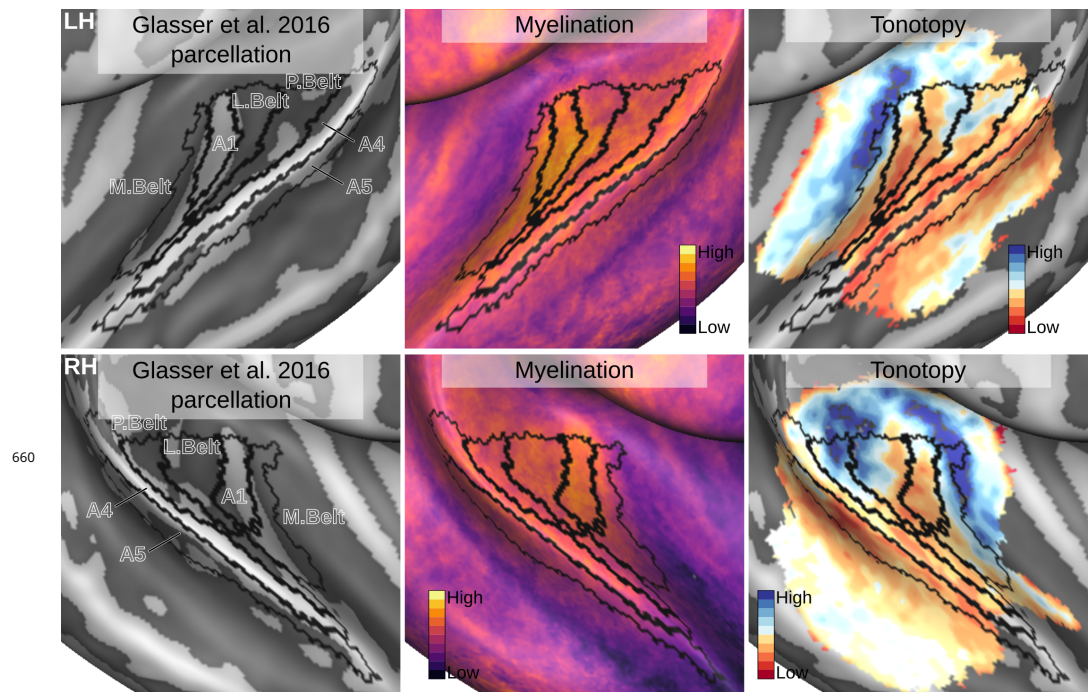


Figure 10-Figure supplement 1. Relation between the in vivo MRI measures of the left hemisphere and the multi modal MRI based parcellation. The multi modal MRI based parcellation from *Glasser et al. (2016)* is delineated with black lines. The myelination index is computed from the division of T_1w and T_2^*w data. Tonotopy reflects the voxel-wise frequency preference estimated with fMRI encoding from the response to natural sound stimuli. All measures are sampled on the middle gray matter surfaces.