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# 1 **Enhancer locus in ch14q23.1 modulates brain asymmetric temporal** 2 **regions involved in language processing**

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8 IMAGEN consortium contributed to replication data; Y.L.G., F.L., C.P., J.F.M., G.D.L and V.F. analyzed  
9 the results; and Y.L.G., C.P., G.D.L. and V.F. wrote the paper.

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## 13 **Abstract**

14 Identifying the genes that contribute to the variability in brain regions involved in language processing may  
15 shed light on the evolution of brain structures essential to the emergence of language in Homo sapiens. The  
16 superior temporal asymmetrical pit (STAP), which is not observed in chimpanzees, represents an ideal  
17 phenotype to investigate the genetic variations that support human communication. The depth of the left  
18 STAP was significantly associated with an enhancer located in the 14q23.1 locus, between *DACT1* and  
19 *KIAA0586*, in the UK Biobank British discovery sample (N=16,515). This association was replicated in the  
20 IMAGEN cohort (N=1,726) and the UK Biobank non-British validation sample (N=2,161). This genomic  
21 region was also associated to a lesser extent with the right STAP depth and the formation of sulcal  
22 interruptions, *plis de passage*, in the bilateral STAP but not with other structural brain MRI phenotypes,  
23 highlighting its notable association with the superior temporal regions. Diffusion MRI emphasized an  
24 association with the fractional anisotropy of the left auditory fibers of the corpus callosum and with networks  
25 involved in linguistic processing in resting-state functional MRI. Overall, this evidence demonstrates a  
26 specific relationship between this locus and the establishment of the superior temporal regions that support  
27 human communication.

## 28 Introduction

29 Which genes participate in the biological foundations of human language processing? This question remains  
30 unanswered. Initial approaches sought to identify rare monogenic mutations in families with language and  
31 speech disorders, which revealed the roles of *FOXP2* (Fisher et al. 1998) and *KIAA0319* (Francks et al.  
32 2004), for example. The discovery of these genes led to productive research in humans and animals in the  
33 following aspects: First, which brain areas do these genes modulate either structurally or functionally in  
34 humans; and second, how do animal variants and even human variants in animals affect neural networks  
35 and animal abilities? A complementary approach, which is now possible due to genotyping and  
36 neuroimaging in large cohorts, is to investigate the relationship between certain brain structures and allelic  
37 variations in the normal human population (Cai et al. 2014). Although all participants have language ability,  
38 this type of research can pinpoint particular genetic and neural architectures, opening new windows to  
39 understanding language. For example, Dediu and Ladd (Dediu and Ladd 2007) proposed that typological  
40 features of languages may depend on certain allele frequencies in human groups, and they explored the  
41 relationship between tonal languages and the distribution of allelic variants of *ASPM* and *Microcephalin*.  
42 Functional and structural asymmetries may be one of the human brain phenotypes whose genetic study may  
43 shed light on this issue. Indeed, human communication is based on the retrieval of two crucial types of  
44 information in speech, who speaks and what is said. In most adults, the message and the messenger are  
45 processed in parallel in the superior temporal region, with the linguistic message (Mazoyer et al. 1993) and  
46 voice identification (Belin et al. 2000) processed in the left and right hemispheres, respectively. This  
47 channeling is present early in human infants (Dehaene-Lambertz et al. 2002; Bristow et al. 2009). At six  
48 months of gestation, activations to syllables are differently lateralized when preterm infants discriminate a  
49 phonetic change (/ba/ vs /ga/) or a voice change (male vs female) (Mahmoudzadeh et al. 2013). Thus, the  
50 left and right peri-sylvian regions are distinctly functionally organized from the onset of thalamocortical  
51 connectivity. Therefore, this organization occurs before sensory input can shape these regions, suggesting  
52 genetically determined protomaps.

53 These functional asymmetries should be discussed in relation to the notable asymmetries visible at the  
54 macroscopic level and reported near the Sylvian fissure. The Sylvian fissure is more dorsal and oblique in  
55 the right hemisphere, the *planum temporale* is larger in the left hemisphere (Geschwind and Levitsky 1968)  
56 and the right superior temporal sulcus (STS) is deeper than the left (Leroy et al. 2015). Some asymmetries,  
57 such as the shape and location of the Sylvian fissure and the left-right size difference in the *planum*, are  
58 observed in apes (Hopkins et al. 2000), but the STS depth asymmetry is the first macroscopic brain  
59 asymmetry that has been observed only in humans. A 45-mm-long segment located under Heschl's gyrus,  
60 superior temporal asymmetrical pit (STAP), is deeper in the right hemisphere than in the left in 96% of  
61 human infants, children, and adults but not in chimpanzees (Leroy et al. 2015). During gestation, the right  
62 STS appears earlier than the left, similar to many other sulci (Dubois et al. 2008; Habas et al. 2012); however  
63 other left sulci catch up, while the left STS remains shallower than the right STS and is more often  
64 interrupted by one or more *plis de passage* (PPs) (Leroy et al. 2015; Le Guen, Leroy, et al. 2018). The  
65 observation of these structural and functional differences before term age suggests that genetically driven  
66 mechanisms guide the development of peri-sylvian regions to endorse the complexity of verbal and  
67 nonverbal communication in the human species. Because of the sharp distinction between chimpanzees and  
68 humans, Leroy et al. (2015) suggested that the STAP may represent an important macroscopic marker of  
69 the recent cytoarchitectonic changes (Cantalupo and Hopkins 2001) in the primate lineage supporting the  
70 communication function in humans. We have previously examined the heritability (i.e., the genetic

71 proportion in phenotypic variance across individuals) of STS characteristics. Because sulcal pits correspond  
72 to the deeper parts of sulci where the initial or primary folds occur, they show less intersubject variability  
73 (Meng et al. 2014; Le Guen, Auzias, et al. 2018). In the left STAP area, the two sulcal pit regions (STS b  
74 and c in Le Guen, Auzias, et al. (2018)) are highly heritable, in contrast to the right STS, yielding the largest  
75 asymmetric estimate of heritability for all brain sulci. In addition, the PPs that interrupt some sulci are more  
76 frequent and heritable in the left STS ( $h^2 = 0.53$ ) than in the right ( $h^2 = 0.27$ ) (Le Guen, Leroy, et al. 2018).  
77 In most brain regions, this interhemispheric difference in heritability estimates was not detected, therefore  
78 suggesting a distinctive genetic modulation in the superior temporal lobes.

79 Therefore, to clarify the genetic influence on the development of the human communication system, we  
80 studied the genetic variants that are significantly associated with STAP phenotypes (i.e., the right and left  
81 sulcal depths, their asymmetry and the formation of PPs). We took advantage of the most recent release of  
82 the UK Biobank, which includes approximately 22,000 individuals genotyped and scanned with the same  
83 MRI scanner and imaging protocol (Miller et al. 2016). We used 16,515 genetically confirmed individuals  
84 of British ancestry as our discovery sample and the remaining 2,161 non-British ancestry subjects as a first  
85 replication sample. In addition, we used the IMAGEN cohort of 1,726 adolescents (14-15 years) as the  
86 second replication sample. We found that an intergenic region upstream of *DACT1* located in 14q23.1  
87 modulates STS phenotypes. To further understand the functional role of this region, we first used databases  
88 of information on gene tissue expression and chromatin states in various brain tissues at different stages of  
89 development. Second, we investigated the effect of this region on brain phenotypes by taking advantage of  
90 the multimodal sequences acquired in the same UK Biobank subjects (T1w, diffusion tensor imaging (DTI)  
91 and resting state). We observed that this gene has a localized effect on the superior temporal regions,  
92 particularly on the left STS, which suggests a role in the establishment of the linguistic network.

## 93 **Methods**

94 **Subjects.** In this study, we used the UK Biobank data released in October 2018, including 22,392 subjects  
95 with T1-weighted MRI who were aged 44 to 81 years at the time of the imaging visit. The genetic data have  
96 already been subject to rigorous quality control (Bycroft et al. 2018). We limited our analysis to individuals  
97 identified by the UK Biobank as belonging to the main subset of white British ancestry. Subjects with high  
98 genotyped missingness, high heterozygosity or sex mismatches were excluded from our analysis (Bycroft  
99 et al. 2018). Briefly, the UK Biobank contains genotypes of 488,377 participants who were genotyped on  
100 the following arrays: UK BiLEVE Axiom Array (807,411 markers; 49,950 participants) and UK Biobank  
101 Axiom Array (825,927 markers; 438,427 participants). The two arrays are very similar, sharing  
102 approximately 95% of the marker content. Genotypes were called from the array intensity data in 106  
103 batches of approximately 4700 samples each using a custom genotype-calling pipeline.

104 Among individuals with the STAP phenotype, 13,956 individuals of British ancestry were scanned at  
105 Cheadle and 2,559 at Nottingham, while, 1,935 individuals of non-British ancestry were scanned at Cheadle  
106 and 226 at Nottingham. In addition, we described previous results obtained with the HCP cohort (Le Guen,  
107 Leroy, et al. 2018), and details are included in **Supplementary Methods**.

108 **Ethical approval.** UK Biobank has approval from the North West Multi-centre Research Ethics Committee  
109 (MREC), which covers the UK. The present study was approved by the UK Biobank ethics committee under  
110 application number 25251.

111 **Imputation.** Phasing and imputation were carried out by the UK Biobank and are described in detail  
112 elsewhere (Bycroft et al. 2018). Briefly, phasing on the autosomes was performed using SHAPEIT3  
113 (O’Connell et al. 2016) with the 1000 Genomes Phase 3 dataset as a reference panel. For imputation, both  
114 the Haplotype Reference Consortium (HRC) reference panel (McCarthy et al. 2016) and a merged  
115 UK10K/1000 Genomes Phase 3 panel were used. This imputation resulted in a dataset with 92,693,895  
116 autosomal SNPs, short indels and large structural variants. This customized imputation represents the most  
117 reliable high-resolution imputation to date and enables fine-mapping to identify causal genetic variants  
118 (Schaid et al. 2018).

119 **Quality control and filtering.** QC was performed using PLINK v1.9<sup>18,19</sup>. We removed all SNPs with a call  
120 rate < 90% accounting for the two genotyping platforms used to genotype individuals (784,256 genotyped  
121 variants remained). In the genotyped variants, we removed variants with more than 5% missing genotype  
122 data (70,737 variants removed), variants with Hardy-Weinberg exact test < 10<sup>-6</sup> (18,462 variants) and  
123 variants with minor allele frequency < 0.01 (101,839 variants). A total of 593,218 genotyped variants  
124 remained for analysis. The same thresholds were applied to the imputed SNPs, and 8,011,919 imputed  
125 variants remained after filtering.

126 In addition, we excluded all individuals who fulfilled at least one of the following criteria: discrepancy  
127 between genetically inferred sex (Data field 22001) and self-reported sex (Data field 31), outliers in  
128 heterozygosity and missing rates (Data field 22027), and individuals not flagged by UK Biobank as  
129 belonging to a white British ancestry subset (Data field 22006) (i.e., identified as British by principal  
130 component analysis and self-reported ‘British’).

131 **MRI data acquisition.** The MRI data acquisition parameters and preprocessing are described in detail in  
132 the UK Biobank Brain Imaging Documentation (v.1.5, August 2018) and in previous UK Biobank  
133 publications describing imaging phenotypes and QC (Miller et al. 2016; Alfaro-Almagro et al. 2018; Elliott  
134 et al. 2018).

135 Briefly:

- 136 • T1 images were acquired with 1 mm isotropic resolution (key parameters: 3D MPRAGE, sagittal,  
137 R=2, T1/TR = 880/2000 ms, duration = 4 min:54 s);
- 138 • T2 FLAIR images were acquired with a 1.05\*1.0\*1.0 mm resolution (key parameters: FLAIR, 3D  
139 SPACE, sagittal, R = 2, PF 7/8, fat sat, T1/TR = 1800/5000 ms, elliptical, duration 5 min:52 s);
- 140 • diffusion MRI (dMRI) images were acquired with 2.0 mm isotropic resolution (key parameters: MB  
141 = 3, R = 1, TE/TR = 92/3600 ms, PF 6/8, fat sat, b = 0 s/mm<sup>2</sup> (5x+ 3\*phase-encoding reversed), b  
142 = 1000 s/mm<sup>2</sup> (50\*), b = 2000 s/mm<sup>2</sup> (50\*), duration = 7 min:8s);
- 143 • resting-state functional MRI (rfMRI) images were acquired with 2.4 mm isotropic resolution (key  
144 parameters: TE/TR = 39/735 ms, MB = 8, R = 1, flip angle = 52°, fat sat, duration = 6 min:10 s).

145  
146 **STAP depth extraction.** The STAP section was extracted using the automated method described in Le  
147 Guen, Leroy, et al. (2018). Briefly, we first extracted the sulcal pits (primary cortical folds) using a  
148 watershed algorithm (Auzias et al. 2015). Then, we summed all the individual pit densities on a symmetric  
149 template using surface-based interhemispheric registration (Greve et al. 2013). We used a watershed  
150 algorithm on this group pit density, which yielded a group parcellation of the sulcal pits. We projected these  
151 group areas onto the individual meshes and identified areas denoted STS b, c, d (Le Guen, Auzias, et al.

152 2018). Then, we extracted the geodesic path of the vertices that follow the sulcal fundus on the white mesh  
153 between the deepest pits STS b and the STS c/d border, which approximately correspond to the STAP  
154 Talaraich coordinates defined by Leroy et al. (2015). From this set of vertices, we obtained individual  
155 profiles of the geodesic depth and depth potential function (PF), which considers both sulcal depth and  
156 convexity. We averaged these values along the STAP for each subject to obtain our depth phenotypes. We  
157 also applied the PP detection method described in Le Guen, Leroy, et al. (2018) and benchmarked on  
158 manually labeled data from Leroy et al. (2015) to identify subjects with at least one sulcal interruption in  
159 their depth profile. This process led to the binary phenotype “presence or absence of PP”. Among our British  
160 discovery sample that completed the pipeline (16,515 subjects), 9,501 subjects had a left PP (57.53%), and  
161 2,587 had a right PP (15.66%). We defined the asymmetry index as  $2(L-R)/(L+R)$ .

162 **Phenome-wide analysis.** We processed the T1w and T2w images with the Freesurfer v6 pipeline (Fischl  
163 2012), and extracted individual measures from the following output files: ?h.aparc.stats (Desikan  
164 parcellation (Desikan et al. 2006)), ?h.aparc.a2009s.stats (Destrieux parcellation (Destrieux et al. 2010)),  
165 and aseg.stats (subcortical volumes). We processed the T1w images with Brainvisa Morphologist pipeline  
166 (Perrot et al. 2011) and obtained individual sulcus measures per subject. We obtained diffusion MRI and  
167 resting-state MRI phenotypes from the UK Biobank (Miller et al. 2016; Elliott et al. 2018). Briefly, diffusion  
168 MRI measures were extracted using TBSS (Smith et al. 2006) from the ICBM 48 white matter tracts atlas  
169 (Mori et al. 2008). For resting-state fMRI (rfMRI), independent component analysis (ICA) was performed  
170 by the UK Biobank on the first 4,181 participants (Miller et al. 2016). A total of 21 and 55 good components  
171 were identified for 25 and 100 component analyses, respectively (Elliott et al. 2018). These components  
172 were subsequently used for rfMRI acquired in the following subjects. The rfMRI phenotypes include the  
173 amplitude of the ICA weighted rfMRI BOLD signal, referred to as ICA amplitude, the Pearson correlation  
174 and partial correlations between pairs of ICA time series, which are also referred to as functional  
175 connectivity.

176 **Quantitative genetics.** In our discovery sample, we used genome complex trait analysis (GCTA), (Yang et  
177 al. 2011) which provides an estimate of heritability in population studies with unrelated genotyped  
178 participants. To compute the kinship matrix of the population, we selected specific SNPs with PLINK v1.9  
179 (Purcell et al. 2007) using the following thresholds: missing genotype = 5% (70,737 variants excluded),  
180 Hardy-Weinberg equilibrium test ( $hwe = 10^{-6}$ ) (18,462), and minor allele frequency ( $maf = 1.0\%$ ) (101,839).  
181 We kept the SNPs in moderate linkage disequilibrium with a variation inflation factor of 10 within a window  
182 of 50 SNPs (91,496 variants excluded). Then, we computed the genetic relationship matrix with GCTA  
183 1.25.3 using the 501,722 SNPs left. The amount of phenotypic variance captured by this matrix is estimated  
184 using a mixed-effects linear model. As covariates, we included gender, genotyping array type, age at the  
185 MRI session and the 10 genetic principal components (PCs) provided by the UK Biobank to account for  
186 population stratification.

187 **Heritability replication in the HCP cohort.** The heritability estimates for the Human Connectome Project  
188 followed the steps described in our previous study (Le Guen, Leroy, et al. 2018). Briefly, these estimates  
189 are computed using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) (Almasy and Blangero  
190 1998) on an extended pedigree of 820 Caucasian individuals, which includes twins and siblings. To replicate  
191 heritability estimates of the STAP phenotypes, we included 820 subjects (383/437 M/F) labeled as  
192 Caucasian with 69 individuals from the Hispanic ethnicity. The pedigree is composed of 191 twin pairs (127  
193 monozygotic (MZ) with 123 siblings and 64 dizygotic (DZ) with 64 siblings and 1 half sibling), 190 siblings,

194 1 half sibling and 59 unpaired individuals, aged between 22 and 36 years old ( $\mu \pm \sigma = 29.0 \pm 3.6$  years). The  
195 pedigree was provided by the HCP, and most sibling pairs were genetically confirmed. Note that in (Le  
196 Guen, Leroy, et al. 2018), we only reported in the main text the heritability of the PPs. However, these were  
197 extracted in each individual based on their STAP geodesic depth and depth PF; thus, to obtain the other  
198 STAP features, we averaged these depth profiles and computed their asymmetry index in the same set of  
199 subjects and used the same methodology to estimate the heritability.

200 **Genome-wide associations in the UK Biobank.** The analyses of genotype-phenotype associations were  
201 performed with PLINKv1.9 (Purcell et al. 2007) using the imputed genotype data. The same thresholds as  
202 above were applied (missing genotype: 5%, hwe:  $10^{-6}$ , and maf: 0.01). We included the same covariates as  
203 those in the quantitative genetics section. For association with the lead SNP, we controlled a posteriori for  
204 the MRI scanner center and brain volumes (**Tables S3-S4**). These two covariates do not affect the main  
205 result presented here.

206 **GWAs replication in the IMAGEN cohort.** For the replication of GWAS, we included 1726 subjects with  
207 T1 MR Images (ADNI-MPRAGE whose parameters are available in (Schumann et al. 2010)) and  
208 genotyping data. The SNPs common to the Illumina 610-Quad and 660-Quad arrays were considered and  
209 we used the imputed data available from the IMAGEN project (<https://imagen2.cea.fr>). Briefly, imputation  
210 was performed using MaCH using the 1000 genome Phase 3 dataset as a reference (v3.20101123).

211 **Functional annotation.** The functional annotations of loci were provided by FUMA (Watanabe et al. 2017),  
212 which notably annotates SNP location, expression quantitative trait loci (eQTL) querying the Braineac  
213 (Ramasamy et al. 2014), GTEx (GTEx Consortium 2017), Common Mind (CMC) (Fromer et al. 2016), and  
214 eQTLGen (Võsa et al. 2018) databases, and splicing QTL (sQTL) in GTEx. GTEx, Braineac and eQTLGen  
215 were further manually queried. Additionally, we queried the Brain-eMeta eQTL summary data (Qi et al.  
216 2018), which is a set of eQTL data from a meta-analysis of GTEx brain (GTEx Consortium 2017),  
217 CMC (Fromer et al. 2016), and ROSMAP (Ng et al. 2017). The estimated effective is  $n = 1,194$  samples.  
218 Only SNPs within a 1Mb distance from each probe are available. This dataset is available on the SMR  
219 website ([cnsgenomics.com/software/smr](https://cnsgenomics.com/software/smr)). The chromatin state was from the Roadmap Epigenomics  
220 Consortium (Roadmap Epigenomics Consortium et al. 2015) and inferred by ChromHMM (Ernst and Kellis  
221 2012) in various brain tissues.

## 222 **Results**

223 **Heritability and genome-wide association.** The first two columns in **Table 1** present the heritability  
224 estimates of STAP phenotypes in the following populations: the extended pedigree of the Human  
225 Connectome Project (HCP) using SOLAR (Almasy and Blangero 1998) and unrelated individuals in the  
226 UK Biobank using GCTA (Yang et al. 2011). Although weaker due to the different cohort design, the higher  
227 heritability estimates in the left hemisphere of the geodesic depth and presence of PP previously obtained  
228 in HCP (Le Guen, Leroy, et al. 2018) were reproduced in UK Biobank individuals (details in **Table S1**).  
229 The depth asymmetry index was also heritable. We computed the genome-wide association (GWA) with  
230 these phenotypes in the UK Biobank discovery sample (see **Fig. S1-S3** for the Manhattan and QQ plots of  
231 these association tests). A region upstream (26.5 kb) of the *DACT1* gene in the cytogenetic band 14q23.1  
232 contains SNPs whose associated p-values passed the Bonferroni-corrected genomic threshold ( $p < 5 \cdot 10^{-8}/8$   
233  $= 6.25 \cdot 10^{-9}$ ) (**Fig. 1A**). **Fig. S4** presents the associated region corresponding to 2 MB around the locus. The  
234 strongest association in imputed SNPs was with rs160458 ( $p = 2.0 \cdot 10^{-12}$ ,  $N = 16,203$ , base pair (bp) position

235 = 59074878 (GRCh37)) and in genotyped SNPs with rs160459 ( $p = 4.2 \cdot 10^{-12}$ ,  $N=16,515$ , base pair position  
236 = 59074136), which are both annotated in Ensembl (Zerbino et al. 2018) as “human-specific bases”.  
237 Suggestive associations ( $10^{-6} < p < 10^{-8}$ ) were observed for other left/right STAP phenotypes, while the  
238 asymmetry index of the geodesic depth and DPF were significant at  $p < 0.05$  (uncorrected). In the following  
239 section, we focus on the genotyped SNP rs160459 because its chromatin state in the brain appears more  
240 consistent with a regulatory role (**Fig. 1B**), and both SNPs are in strong linkage disequilibrium ( $r^2 = 0.936$   
241 in British ancestry, distance in build GRCh37 = 742 bp).

242 **Replication of the association in two other populations** (**Table 1** for rs160459 and **Table S2** for  
243 rs160458). The association with the STAP left geodesic depth was replicated in the two samples above the  
244 nominal significance level ( $p < 0.05$ ), with  $p = 8.0 \cdot 10^{-5}$  in the IMAGEN cohort and  $p = 0.041$  in the non-  
245 British UK Biobank sample. On average, the allelic repartition across the three population samples is 21.6%  
246 ‘CC’, 49.9% ‘CA’, and 28.5% ‘AA’. **Fig. S5** illustrates the effect size of the rs160459 allelic configuration  
247 on the geodesic depth and depth PF in the three populations revealing shallower STS in the ‘AA’ allelic  
248 configuration. **Fig. 2A** shows the influence of rs160459 along the STAP geodesic depth profile. Its allelic  
249 configuration exerts a strong control on the posterior part of the left STAP notably at the average location  
250 of the posterior PP when it exists.

251 **Role of the rs160459 region in the regulation of nearby genes.** **Fig. 1B** presents the chromatin state  
252 functional annotation of the genomic region upstream of *DACT1* (i.e., the region significantly associated  
253 with the left STAP geodesic depth). The subregion around rs160459 has its chromatin state in brain tissues  
254 annotated as enhancer (Enh) and/or flanking active transcription start site (TssAFlnk) (Ernst and Kellis  
255 2012; Roadmap Epigenomics Consortium et al. 2015), thus revealing its active chromatin state in all tested  
256 brain areas, with the notable exception of the dorso-lateral prefrontal cortex. In contrast, this region has a  
257 quiescent chromatin state in most other body tissues except stem cells and epithelial cells, suggesting a  
258 tropism for neuro-ectoderm derived cell lines (**Fig. S6**). **Table S5** provides the eQTL query results in Brain-  
259 eMeta for the genome-wide significant (GWS) hits. We did not find any significant eQTLs in brain tissues  
260 among our GWS SNPs in Brain-eMeta, except rs10782438 which eQTL of *PSMA3-ASI* ( $p_{\text{uncorrected}} = 7 \cdot 10^{-5}$ ,  
261  $p_{\text{FDR}} = 0.05$ ). Querying eQTLGen, which includes a large number of subjects with gene expression in blood,  
262 rs160459 is an eQTL of *DACT1* ( $p_{\text{uncorrected}} = 9 \cdot 10^{-5}$ ,  $N = 30,757$ ) but not of other protein coding genes, with  
263 a decrease in *DACT1* expression with rs160459-C. Additionally, one of the GWS SNPs, rs10782438, is a  
264 FDR significant eQTL of *DACT1* ( $p_{\text{uncorrected}} = 5 \cdot 10^{-7}$ ,  $N = 31,086$ ,  $p_{\text{FDR}} = 0.01$ ) (**Table S6**). In British  
265 ancestry, according to LDlink, rs160459 and rs10782438 are in strong linkage disequilibrium with  $r^2 =$   
266  $0.9132$  and  $D' = 0.9772$ . Additionally, we note in GTEx that rs160459 and several SNPs of the GWS locus  
267 block are splicing QTLs (sQTLs) of *KIAA0586* and *PSMA3-ASI* in several non-brain tissues (**Table S7**).

268  
269 **Nearby gene expression across the lifespan.** **Fig. S7** presents the expression levels of genes within +/- 1  
270 MB of the GWS locus, across brain developmental stages, from Brainspan (Miller et al. 2014). Among these  
271 genes, *ACTR10*, *RTNI* and *DACT1* showed the highest expression level, with *RTNI* mainly expressed in  
272 brain tissues (GTEx data not shown). The normalized expression of the genes at least moderately expressed  
273 in the brain is reported in **Fig. 1C**. We note that *DACT1* and *DAAMI* are mainly expressed during early  
274 brain development in the following distinct periods: high expression from the early to late mid-prenatal  
275 period (8 to 24 weeks post-conception (pcw), no data before 8 pcw), followed by a decrease from the late  
276 prenatal period (26 pcw) until the end of the first year, and minimal expression after early childhood (from



277 2 years of age). *KIAA0586* is mainly expressed during the early prenatal period (8 to 12 pcw), while *PSMA3-*  
278 *ASI* has a similar trend with an expression level peak during the late-mid prenatal period (16-17 pcw).

279  
280 **Association of multimodality MRI phenotypes association with rs160459.** To characterize the potential  
281 role of this enhancer genomic region in shaping the human brain, we performed a phenome-wide association  
282 (PheWA) of rs160459 with various brain phenotypes computed on structural, diffusion and functional MRI  
283 exams available from the UK Biobank. We extracted (i) the brain sulci features with Morphologist (Perrot  
284 et al. 2011); (ii) cortical thickness, surface area and gray matter volumes with Freesurfer on the Desikan  
285 (Desikan et al. 2006) and Destrieux (Destrieux et al. 2010) atlases; and (iii) the subcortical volumes with  
286 Freesurfer. From the UK Biobank, we obtained (iv) tract-based spatial statistics (TBSS) (Smith et al. 2006)  
287 on white matter tracts from the ICBM atlas (Mori et al. 2008) and (v) resting-state functional MRI (rfMRI)  
288 phenotypes (see Methods).

289 **Table 2** summarizes the 20 phenotypes with the strongest associations (smallest p-values) with rs160459  
290 (**Table S8** for rs160458, **Table S9** with all phenotypes for rs160459). The Bonferroni significance threshold  
291 was  $p < 9.7 \cdot 10^{-6}$  (0.05/5179 phenotypes, strict correction not accounting for correlations between  
292 phenotypes). A majority of phenotypes are directly related to lateral and superior parts of the temporal  
293 cortex, notably the left STS (depth, gray matter volume, surface area and thickness of its banks).

294 **Fig. S8** shows the mapping of the p-values of the association between rs160459 and brain sulci features  
295 (maximum depth, mean depth, sulcal width, surface, gray matter thickness along the sulcus, and sulcus  
296 length). This genetic variant clearly has a localized effect on the superior temporal region curvature, with  
297 an effect on both the left and right STS as well as on the anterior inferior temporal sulcus. Similarly,  
298 regarding cortical features obtained from Freesurfer parcellations (gray volume, surface area, and cortical  
299 thickness), the effect is localized to the temporal regions, notably the left banks of the STS in the Desikan  
300 atlas (**Fig. S9**) and the left temporal pole and the middle temporal gyrus in the Destrieux atlas (**Fig. S10**).

301 Two main associations were uncovered with diffusion MRI analysis. The most significant association was  
302 with the fractional anisotropy (FA) measured in the left tapetum of the corpus callosum, and the second  
303 corresponded to the mode of anisotropy (MO) of the left cerebellar peduncle.

304 Finally, we analyzed resting-state activity. rs160459 modulates several components that comprise linguistic  
305 regions (**Fig. S11**,  $p < 0.01$ , uncorrected), such as the superior temporal regions, the insula, the inferior  
306 frontal region and the basal ganglia (component 18 for ICA25; and components 9 and 38 for ICA100).  
307 Associations with ICA100 amplitudes included the left fusiform and associative visual areas (components  
308 52 and 8, respectively). Correlations between resting-state networks revealed associations with components  
309 29-41 and 8-31 for ICA100 and 5-18 for ICA25 (**Fig. S12**), which are implicated in language processing  
310 (**Fig. S13**). In particular, **Fig. 3A** presents the most associated pair, 29-41, with rs160459. Notably,  
311 component 29 bilaterally comprises the angular and supra-marginal gyri, the STAP and the posterior  
312 cingulate. Component 41 includes a string of areas from Brodmann area 19 and the fusiform gyri to the  
313 posterior STS.

314 **Characterizing the local influence of rs160459 on brain anatomy.** The ‘CC’ and ‘AA’ allelic  
315 configurations were observed in a roughly similar number of subjects. We compared brain anatomy (DTI  
316 FA values, sulcal depth and thickness values) in ‘CC’ vs ‘AA’ subjects. A voxelwise difference in FA values  
317 in the MNI space was detected between the 4,742 British subjects with the ‘AA’ allele and the 3,470 subjects  
318 with the ‘CC’ allele (**Fig. 3C**, left). These regions are projected on the cortex in **Fig. 3C** (right). The tapetum,  
319 which comprises the auditory callosal fibers, is delineated bilaterally, in addition to a region close to the  
320 hippocampus. We also noted a difference in FA in the left STS region at the average boundary between gray

321 and white matter, which corresponds to the average location of the posterior PP in the STAP when present.  
322 Similarly, **Fig. 3B** highlights the vertexwise difference in sulcal depth between ‘AA’ and ‘CC’ individuals  
323 (other configuration differences are shown in **Fig. S14**). The left STAP clearly appears as the region with  
324 the most substantial difference in depth between these two groups of individuals. Two other areas display  
325 reverse effects relative to the STAP; the first area is in the left intraparietal sulcus, and the second is in the  
326 left inferior temporal gyrus along the STAP. In the posterior part of the left STAP relative to ‘CC’ subjects,  
327 ‘AA’ subjects have a shallower sulcus surrounded by more pronounced gyri, whereas the white matter is  
328 more isotropic under the sulcus and anisotropic under the *planum temporale* and the middle temporal gyrus.  
329 The vertexwise gray matter thickness difference between ‘AA’ and ‘CC’ subjects did not produce  
330 remarkable differences, although a small cluster in the left inferior temporal gyrus along the STAP is notable  
331 (**Fig. S15**).

## 332 **Discussion**

333 **A genomic effect focused on the language comprehension network.** We explored the genetic associations  
334 of a recent evolutionary brain feature, the asymmetry of the depth of the STS, and found that the depth of  
335 the left STS was heritable in two different population samples (HCP, UK Biobank from British ancestors)  
336 and associated with a genomic region upstream of *DACT1*. This genomic region modulates several other  
337 features of the left STS (the gray matter volume, thickness and surface areas of its banks) and of close brain  
338 parcels within the left auditory/linguistic network (i.e., Jensen sulcus at the border between the supra-  
339 marginal and angular gyri, Heschl’s gyrus volume and thickness of the left middle temporal lobe), as well  
340 as, to a lesser extent, their right homologues (i.e., STS depth and thickness). Notably, although we started  
341 from an asymmetric feature, rs160459 associations with brain phenotypes were often significant in both  
342 hemispheres. However, the most apparent effects were always observed in the left hemisphere. As  
343 summarized in **Fig. 3C**, this SNP mainly modulated the macro- and microstructure of the temporal and  
344 supra-marginal components of the linguistic network with an effect limited to the left STS for some  
345 phenotypes, such as sulcal depth (**Fig. S7-S11**). This tropism for the auditory/linguistic regions was  
346 confirmed by resting-state analyses. rs160459 modulated the amplitude of components comprising the  
347 classical language areas (superior temporal and inferior frontal regions and the basal ganglia), as indicated  
348 by the correlation between two resting-state components (ICA100: 29-41,  $p \sim 10^{-6}$ ). The ICA recovers  
349 bilateral components, making it difficult to disentangle the contribution of each hemisphere. Nonetheless,  
350 in the left hemisphere, the correlation between components 29-41 is reminiscent of the ventral and dorsal  
351 pathway of the reading network. This interpretation related to reading would also be consistent with the  
352 significant modulation of the amplitude of the left fusiform gyrus (ICA100: component 52). The relationship  
353 between this genomic region and language is also supported by two patients with a 14q23.1 deletion who  
354 had moderate to severe expressive language delay (Jiang et al. 2008; Martínez-Frías et al. 2014).

355 An interesting structure was also highlighted in our analyses: the left tapetum, i.e., the auditory fibers of the  
356 corpus callosum. This result may be associated with the observation that patients with corpus callosum  
357 agenesis are also the only group with no significant STS depth asymmetry in Leroy et al. (2015). The authors  
358 speculated that the dense local connectivity useful for phonetic encoding (DeWitt and Rauschecker 2012)  
359 intertwined with many long-range bundles (Turken and Dronkers 2011) (the callosal auditory fibers but also  
360 the arcuate fasciculus, inferior occipito-frontal fasciculus, and middle and inferior longitudinal fasciculi),  
361 which underlie the left STS and create different tensions and tissue stiffness compared with those in the  
362 right hemisphere, explaining the depth asymmetry of this sulcus. Therefore, the elevation of the bottom of

363 the left sulcus, particularly in its posterior part, could be related to a localized higher fiber density, which  
364 may eventually result in a PP (**Fig. 2, 3B**). Among these tracts, the arcuate fasciculus, which is the most  
365 left-lateralized tract (Dubois et al. 2010), was not directly extracted in our analyses, but the voxelwise  
366 differences between allelic variants below the left STAP could correspond to it.

367 **A role in establishing the auditory/linguistic network.** The locus uncovered by our genome-wide  
368 association is nearest to *DACT1*, a gene mainly active, in human brain tissues, during gestation until the age  
369 of two years, a crucial period for language acquisition and social communication. The protein encoded by  
370 *DACT1* belongs to the dapper family and is involved in regulating intracellular signaling pathways during  
371 development. Among its related pathways is the noncanonical Wnt/planar cell polarity pathway, which is  
372 activated in the neuronal differentiation process (Jiao et al. 2018) and synaptogenesis (Rosso et al. 2013).  
373 *DACT1* is reportedly involved in excitatory synapse organization, dendrite and synapse formation,  
374 establishment of spines in hippocampal pyramidal neurons (Okerlund et al. 2010), and in migration of  
375 cortical interneurons (Arguello et al. 2013). Thus, *DACT1* plays a major role in the morphology of pyramidal  
376 cells and interneurons. Our results suggest that the uncovered locus regulates *DACT1* expression in blood.  
377 Since, blood cis-eQTLs often support cis-eQTLs in brain tissues, providing a sufficient sample size (Qi et  
378 al. 2018), this locus may be an eQTL early in brain development when *DACT1* is most highly expressed.  
379 Additionally, the STS becomes visible at approximately 25-29 wGA (Chi et al. 1977; Habas et al. 2012) -  
380 the right STS appears one or two weeks earlier than the left – at which time the *DACT1* expression level  
381 significantly decreases (**Fig. 1C**). At this age, the majority of neurons remain in the subplate, but the main  
382 tracts (e.g., the corpus callosum and the fronto-occipital fasciculus) become visible. Short-range  
383 connectivity emerges, bending around the bottom of the sulci. The brain begins to process external stimuli,  
384 such as sounds and voices, along distinctive pathways, but as maturation progresses and stimulation  
385 becomes richer, dendrite development and axonal arborization complexify the gyrification pattern,  
386 accentuating the initial hemispheric biases. Furthermore, analyzing sQTL data, the uncovered locus  
387 regulates *PSMA3-AS1* and *KIAA0586* splicing (evidence from non-brain tissues). *PSMA3-AS1* is a *PSMA3*  
388 antisense and has 42 long non-coding RNA transcripts according to LNCipedia. Antisense transcript roles  
389 are generally not well characterized, but it is suggested that they may be involved in the regulation of gene  
390 expression through RNA hybrids that lead to transcriptional interference or even gene silencing (Wight and  
391 Werner 2013). A previous study showed that *PSMA3-AS1* can form an RNA duplex with pre-*PSMA3*, which  
392 promotes *PSMA3* and increases its stability (Xu et al. 2019). *KIAA0586*, also known as *Talpid3*, has 24  
393 transcripts according to the NCBI. Studies in various animal models and humans (see Fraser and Davey  
394 (2019) for review) have shown that *KIAA0586* is required for ciliogenesis (Yin et al. 2009), sonic Hedgehog  
395 signaling (Davey et al. 2006), and the asymmetrical localization of CEP210 to daughter centrioles  
396 (Kobayashi et al. 2014). Additionally, mutations in *KIAA0586* have been linked to Joubert Syndrome  
397 (Bachmann-Gagescu et al. 2015), which is characterized by underdevelopment of the cerebellar vermis and  
398 the molar tooth sign, corresponding to a malformed brain stem.

399 In conclusion, the genomic region in linkage disequilibrium with rs160459 modulates the STS depth and  
400 other related MRI phenotypes in the temporal lobe. Overall, the identified locus contributes to human  
401 variability in the formation of superior temporal networks, especially those involved in language. The link  
402 between this locus and the following three candidate genes should be further investigated: *DACT1*, whose  
403 gene expression in the brain corresponds with the STS formation timeframes; *KIAA0586*, which is required  
404 for sonic Hedgehog signaling and essential for primary ciliogenesis, and whose loss of function causes  
405 ciliopathies; and *PSMA3-AS1* whose function remains largely unexplored.

406 **CONFLICT OF INTEREST.** The authors declare no conflict of interest.

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410

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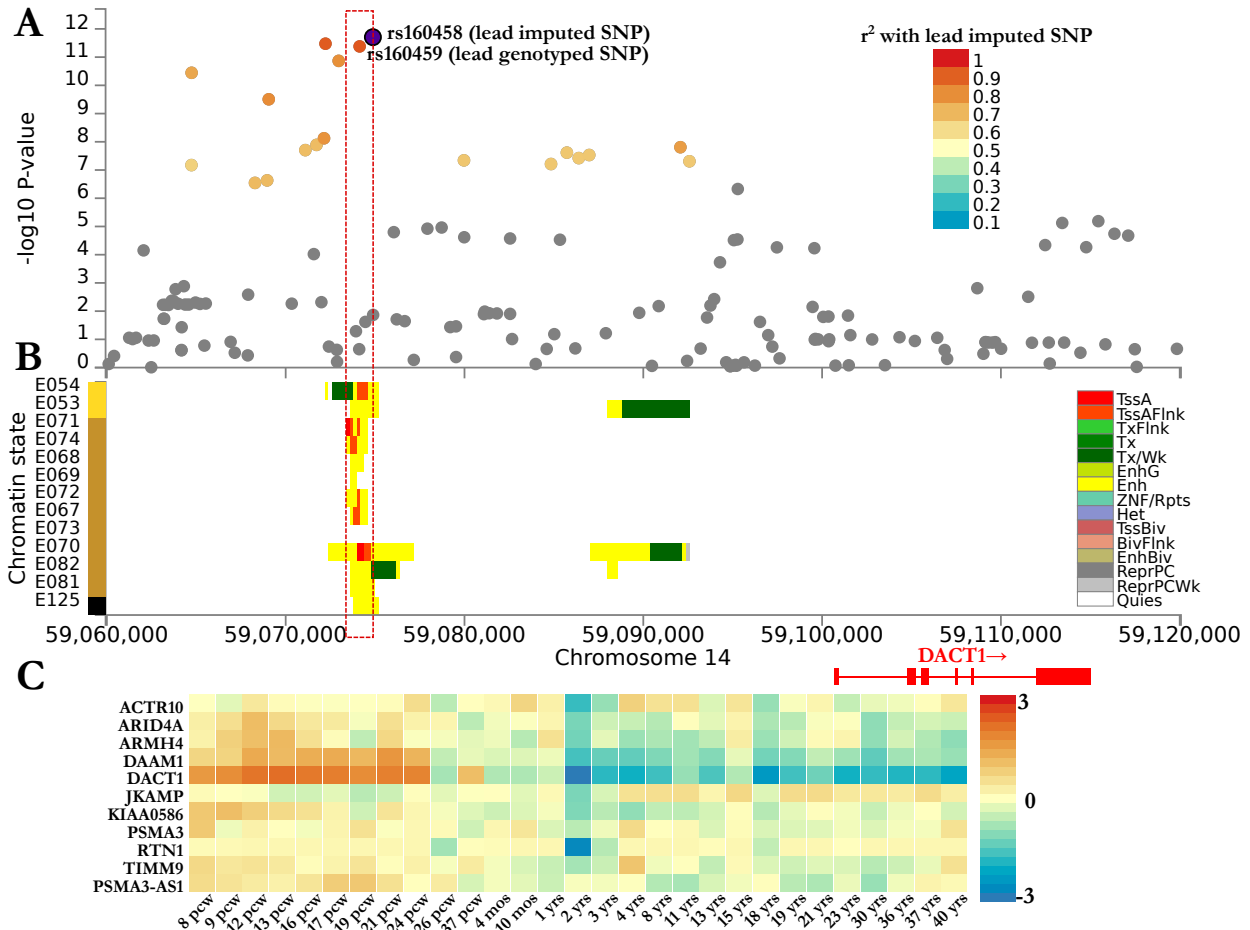
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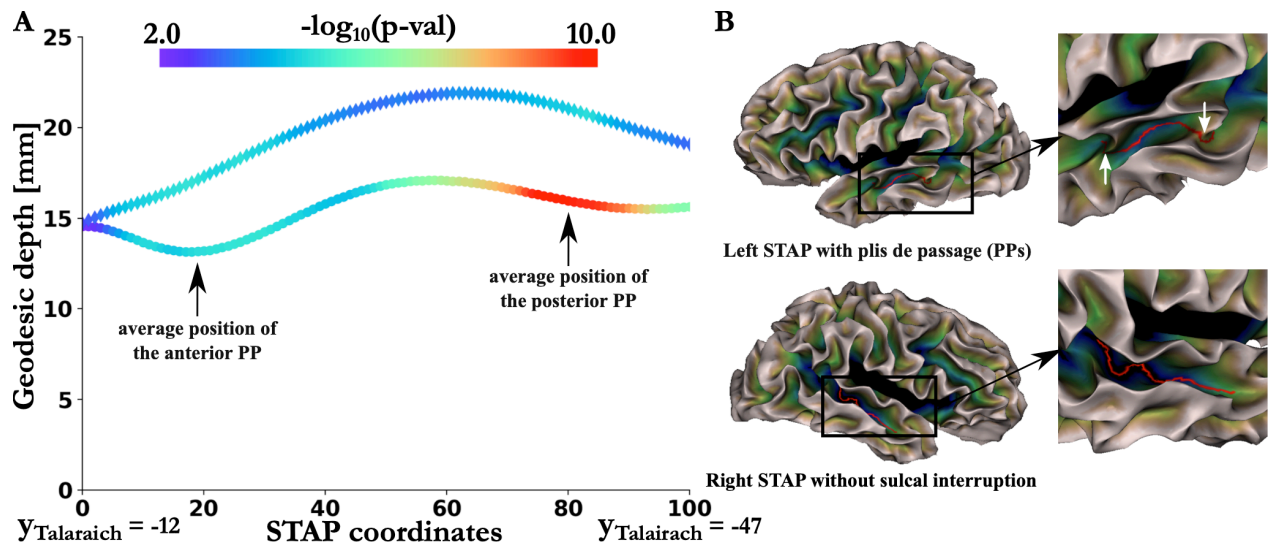
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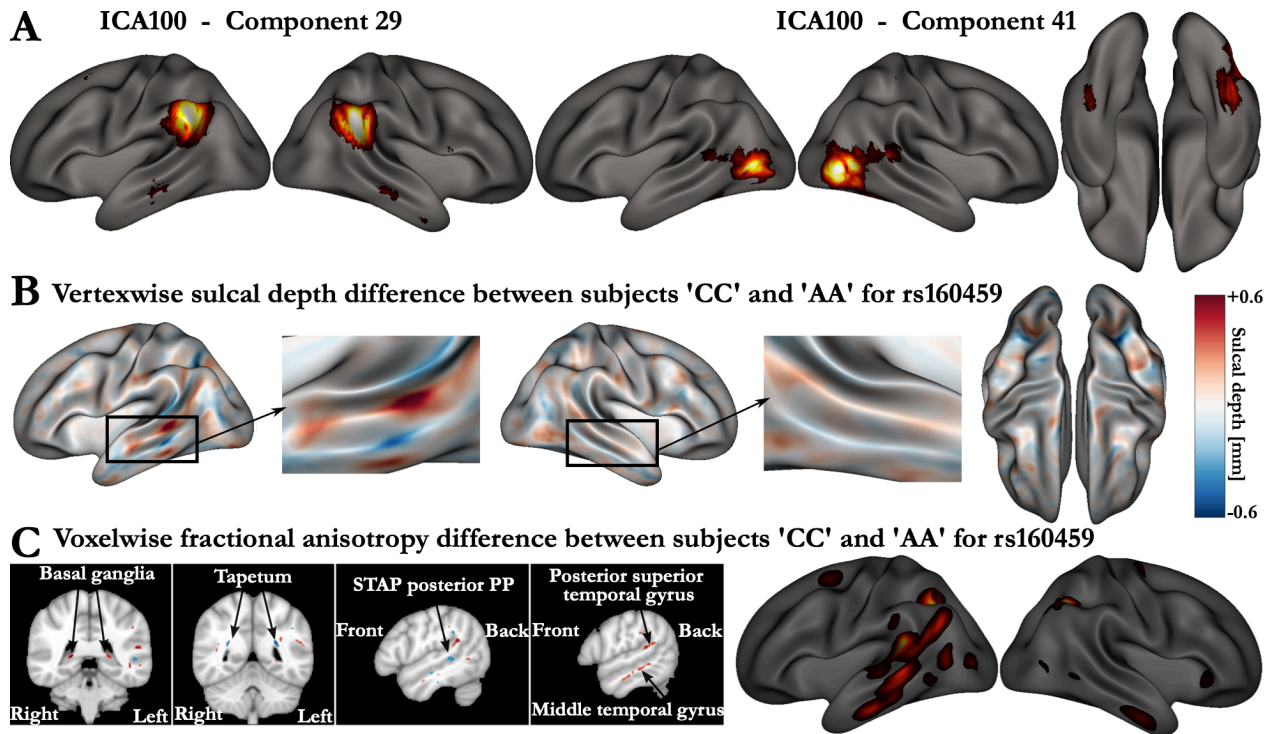
645 **Fig. 1 (A) Manhattan plot of the geodesic depth in the left STAP zoomed in on the significant**  
 646 **associations upstream of the *DACT1* gene (14q23.1). (B) Chromatin state of the genomic region near**  
 647 **lead SNPs rs160458 (imputed) and rs160459 (genotyped). The *DACT1* position and exons are highlighted**  
 648 **in red on the axis showing the base pair position (GRCh37) on chromosome 14. Yellow corresponds to the**  
 649 **enhancer (Enh) state, red-orange to the flanking active transcription start site (TssAFlnk), green to weak**  
 650 **transcription (Tx/Wk) and white to quiescent (Quies) (see ref. (Ernst and Kellis 2012; Roadmap**  
 651 **Epigenomics Consortium et al. 2015) for the complete legend). (C) Average normalized gene expression**  
 652 **(zero mean across samples) of genes +/- 1 MB of rs160459 (Fig. S4, Fig. S7) at 29 developmental ages**  
 653 **from Brainspan (Miller et al. 2014). Brain tissue name abbreviations in (B): E054: Ganglion Eminence-**  
 654 **derived primary cultured neurospheres, E053: Cortex-derived primary cultured neurospheres, E071: Brain**  
 655 **Hippocampus Middle, E074: Brain Substantia Nigra, E068: Brain Anterior Caudate, E069: Brain Cingulate**  
 656 **Gyrus, E072: Brain Inferior Temporal Lobe, E067: Brain Angular Gyrus, E073: Brain Dorsolateral**  
 657 **Prefrontal Cortex, E070: Brain Germinal Matrix, E082: Fetal Brain Female, E081: Fetal Brain Male, E125:**  
 658 **Astrocyte Primary Cells.**

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660

661 **Fig. 2 (A) Mapping of the p-values along the STAP profile averaged over 16,515 British subjects of**  
 662 **the association between rs160459 and geodesic depth.** Left values are represented by disks and right  
 663 values by diamonds (for more details, see Fig. S16). (B) **Example of asymmetries in an individual subject**  
 664 **with anterior and posterior PPs in the left STAP but no PP in the right STAP.** Note that most subjects  
 665 have only one PP either anterior or posterior in the left STAP and no sulcal interruption in the right STAP  
 666 (Le Guen, Leroy, et al. 2018).



667  
 668 **Fig. 3 (A)** ICA100 pair (29-41) for which their full correlation has the most significant association  
 669 **with rs160459. (B)** Vertexwise sulcal depth difference in rs160459 between 'CC' and 'AA' subjects.  
 670 Red values show higher depth values for CC subjects and blue for AA subjects. **(C)** Voxelwise fractional  
 671 **anisotropy difference in rs160459 in the MNI space between 'CC' and 'AA' subjects.** These figures are  
 672 thresholded at 0.005 [unitless fractional measure] to underline the main differences. In the right column,  
 673 these differences in white matter are projected onto the cortex.

674

675 **Table 1. P-values of the association of rs160459 with the STAP phenotypes in three populations.**  
676 \* indicates significant heritability estimates ( $p < 6.3 \cdot 10^{-3}$ , details in Table S1.). AI: asymmetry index =  
677  $2(L-R)/(L+R)$ , PF: potential function, PP: *pli de passage*.  $\beta$  are provided for quantitative phenotypes and  
678 OR for PPs.

Phenotype/Cohort	Heritability		Association - $\beta$ (p-val) and OR (p-val) for PPs		
	HCP	UKB	UKB discovery N=16,515 British	IMAGEN replication N=1,726	UKB replication N=2,161 Non- British
Left STAP geodesic depth	48%*	21%*	<b>0.2683</b> ( $4.2 \cdot 10^{-12}$ )	0.4614 ( $8.0 \cdot 10^{-5}$ )	0.242 (0.0133)
Right STAP geodesic depth	46%*	15%*	0.179 ( $1.3 \cdot 10^{-7}$ )	0.3204 ( $2.2 \cdot 10^{-4}$ )	0.04269 (0.1563)
AI of the STAP geodesic depth	30%*	9%*	0.008638 (0.0017)	0.01226 (0.0406)	0.01355 (0.1675)
Left STAP depth PF	25%*	18%*	0.009865 ( $3.8 \cdot 10^{-8}$ )	0.01265 (0.01)	0.009936 (0.1004)
Right STAP depth PF	38%*	4%	0.004759 ( $4.1 \cdot 10^{-6}$ )	0.005239 (0.0971)	0.004668 (0.0249)
AI of the STAP depth PF	22%*	11%*	0.004949 (0.0053)	0.007321 (0.0909)	0.005525 (0.5414)
PP in the left STAP	53%*	16%*	0.8901 ( $2.7 \cdot 10^{-7}$ )	0.8025 (0.0022)	0.9084 (0.2447)
PP in the right STAP	27%	0%	0.8533 ( $2.6 \cdot 10^{-7}$ )	0.7506 (0.0034)	0.8724 (0.2067)

679

680 **Table 2. Top 20 MRI phenotypes associated with rs160459 (significant after Bonferroni correction  $p$**   
681  **$< 9 \cdot 10^{-6}$ ,  $0.05/5179$ ).** (GM: gray matter, DKT: Desikan-Killiany atlas, DST: Destrieux atlas, rfMRI: resting-  
682 state functional MRI). Color code: orange: **Brainvisa phenotypes**, green: **Freesurfer phenotypes**, blue:  
683 **diffusion MRI phenotypes**, red: **rfMRI phenotypes**.

Phenotypes	Pvals	N subjects (British)
<b>Mean depth of the left STS</b>	$1.4 \cdot 10^{-13}$	18101
Surface area of the left temporal pole - DST	$5.8 \cdot 10^{-12}$	17127
GM volume of the left banks STS - DKT	$7.6 \cdot 10^{-8}$	17127
Surface area of the right cuneus gyrus - DST	$2.3 \cdot 10^{-7}$	17127
Surface area of the left banks STS - DKT	$2.8 \cdot 10^{-7}$	17127
Fractional anisotropy of the left tapetum of corpus callosum	$5.7 \cdot 10^{-7}$	16541
Surface area of the right cuneus - DKT	$6.6 \cdot 10^{-7}$	17127
GM thickness of the right middle temporal gyrus - DKT	$6.9 \cdot 10^{-7}$	17127
GM thickness of the left banks STS - DKT	$8.8 \cdot 10^{-7}$	17127
GM thickness of the left middle temporal - DKT	$1.1 \cdot 10^{-6}$	17127
<b>Maximum depth of the left anterior inferior temporal sulcus</b>	$1.5 \cdot 10^{-6}$	18101
GM thickness of the left middle temporal gyrus - DST	$1.9 \cdot 10^{-6}$	17127
<b>rfMRI correlation between ICA100: 29 and 41 (edge 1146)</b>	$2.1 \cdot 10^{-6}$	15859
<b>Mean depth of the right STS</b>	$2.3 \cdot 10^{-6}$	18100
Surface area of the right temporal pole - DST	$2.4 \cdot 10^{-6}$	17126
GM thickness of the right banks STS - DKT	$6.0 \cdot 10^{-6}$	17127
<b>rfMRI correlation between ICA25: 5 and 18 (edge 87)</b>	$7.6 \cdot 10^{-6}$	15864
GM volume of the left Jensen sulcus - DST	$7.6 \cdot 10^{-6}$	17108
GM volume of the left transverse temporal - DKT	$7.9 \cdot 10^{-6}$	17126
<b>Surface area of the left anterior inferior temporal sulcus</b>	$8.6 \cdot 10^{-6}$	18101

684